Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the available evidence in relation to the potential obesogenic activity of certain chemical compounds that may be present in foods

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Abstract

According to the World Health Organization (WHO), obesity and overweight have reached epidemic proportions globally. In Spain, the prevalence of obesity is high, especially in childhood, with an upward trend in the last two decades. While improving dietary habits and increasing physical activity has been the main focus on reducing obesity, its rapid increase in countries with different dietary habits and physical activity patterns suggests the possible existence of environmental factors, such as exposure to chemicals with obesogenic activity. Obesogens have been defined functionally as

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chemical compounds that promote obesity by increasing the number of adipose cells and/or the accumulation of fat in existing adipocytes. Among the most studied obesogens are substances used in the plastic industry such as bisphenols and phthalates, organotin compounds, flame retardants, perfluorinated compounds, polychlorinated biphenyls and dioxins, pesticides and metals, among others. Because the term obesogens includes a large number of compounds, exposure to them can occur by different routes such as inhalation, dermal exposure or ingestion, the latter being the main route of exposure.

The mechanisms of action of obesogens are diverse, and they can act by activating or antagonizing the action of nuclear hormone receptors that directly regulate the expression of genes involved in the differentiation of adipocytes, body weight and metabolism, such as oestrogen, androgen and thyroid hormone receptors, and the peroxisome proliferator activated receptor-γ, among others. They can also act in the regulation of different immune-neuroendocrine metabolic pathways, which can lead to pathophysiological consequences in adipogenesis, lipogenesis, lipolysis, immunity, in the influence on the central regulations of appetite and energy expenditure, and changes in the intestinal microbiota, among other processes. It is important to highlight that the most critical periods of exposure to obesogens are preconception, pregnancy and childhood given their importance for metabolism, and may result in permanent changes in adolescence and in adulthood.

In this context, the Scientific Committee of the Spanish Agency of Food Safety and Nutrition (AESAN) has carried out a review of the evidence that exists on food exposure to obesogens and its possible effect on health. Scientific literature shows in *in vivo* and *in vitro* studies the obesogenic effect of some chemical compounds present in food, and epidemiological studies reinforce this hypothesis. The Scientific Committee recommends that a greater number of studies be carried out to assess the effect of exposure to these compounds, standardizing biomarkers of exposure and effect in order to predict and evaluate their obesogenic capacity and the possible transmission of the effect to other generations through epigenetic mechanisms. Once all the necessary evidence is available, there must be coordination and communication between scientists, clinicians and national and international regulatory bodies, in order to develop a global and efficient strategy in the implementation of risk management measures to reduce exposure to these substances as much as possible.

Key words

Obesity, obesogens, adipogenesis, bisphenol A and analogues, phthalates, tributyltin, flame retardants, PCBs, PCDDs, PCDFs, perfluorinated, pesticides, metals, triclosan, microplastics.

Suggested citation

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Abbreviations

4-HNE: 4-Hydroxynonenal
6-OH-BDE-47: 6-Hydroxy-2,2',4,4'-tetrabromodiphenyl ether
ADI: Acceptable Daily Intake
AhR: Aryl hydrocarbon
Akt: Protein kinase B
aP2: Activating protein 2
AS3MT: Arsenic 3 Methyltransferase
ASCs: Adipose-Derived Stem Cells
BBP: Butylbenzylphthalate
BMD: Benchmark Dose
BMDL: Benchmark Dose Lower Bound
BMI: Body mass index
BPA: Bisphenol A
BPAF: Bisphenol AF
BPB: Bisphenol B
BPE: Bisphenol E
BPF: Bisphenol F
BPS: Bisphenol S
BzBP: Benzylphthalate
C/EBP: CCAAT/Enhancer-Binding Protein
CBT: Triclocarban
Cl-PFAES: Chlorinated polyfluorinated ether sulphonates
CpG: 5'-C-Phosphate-G-3
DBP: Dibutylphthalate
DBT: Dibutyltin
DDE: Dichloro diphenyl dichloroethylene
DDT: Dichloro diphenyl trichloroethane
Deca-PBDEs: Deca-bromodiphenyl ethers
DEHP: Diethylhexylphthalate
DEP: Diethylphthalate
DEXA: Dual-energy x-ray absorptiometry
DiBP: Diisobutyliphthalate
DiDP: Diisodecylphthalate
DiNP: Diisononylphthalate
DMP: Dimethylphthalate
DOP: Di-n-octylphthalate
DOT: Di-n-octyltin
DPHP: Dipropylphenylphthalate
ER: Oestrogen Receptor

FABP: Fatty acid-binding protein
GLUT4: Glucose transporter type 4
hBMSC: Human bone marrow-derived mesenchymal stem cells
HCB: Hexachlorobenzene
HDL: High-density lipoproteins
Hepta-PBDEs: Hepta-bromodiphenyl ethers
Hexa-PBDEs: Hexa-bromodiphenyl ethers
hMSCs: Human mesenchymal stem cells
HPA-v: Human Preadipocytes-visceral
IRS1: Insulin Receptor Substrate 1
I-TEQ: International toxic equivalent
LB: Lower Confidence Limit
LDL: Low-density lipoproteins
LPL: Lipoprotein lipase
MAPK: Mitogen-activated protein kinase
MBzP: Monobenzylphthalate
MCOP: Mono (carboxyl) phthalate
MEHP: Mono-2-ethylhexylphthalate
miR-29b: MicroRNA 29b-1
MNPs: Micro(nano)plastics
MPs: Microplastics
mRNA: Messenger ribonucleic acid
MSC: Mesenchymal stem cells
mTCS: Triclosan-methyl
NAFLD: Non-alcoholic fatty liver disease
NFkB: Nuclear kappa light chain-enhancing factor of activated B cells
NPs: Nanoplastics
Nrf2: Erythroid factor 2
Octa-PBDEs: Octa-bromodiphenyl ethers
OR: Odds ratio
OTs: Organotins
PBDD/Fs: Polybrominated dibenzo-p-dioxins and furans
PBDEs: Polybrominated diphenyl ethers
PBPK: Physiologically Based Pharmacokinetic Modelling
PCBs: Polychlorinated biphenyls
PCDDs: Polychlorinated dibenzodioxins
PCDFs: Polychlorinated dibenzofurans
PE: Polyethylene
Penta-PBDEs: Penta-bromodiphenyl ethers
Pet: Polyethylene terephthalate

PFAAs: Perfluorinated alkyl acids
PFAs: Perfluorinated compounds
PFBS: Perfluorobutanesulfonic acid
PFHxS: Perfluorohexane sulfonic acid
PFNA: Perfluorononanoic acid
PFOA: Perfluorooctanoic acid
PFOS: Perfluorooctane sulfonic acid
PFUnDA: Fluoroundecanoic acid
PP: Polypropylene
PPARγ: Peroxisome proliferator-activated receptor-γ
PS: Polystyrene
PVC: Polyvinyl chloride
RfDs: Reference doses
RXR: Retinoid receptor X
SREBP: Sterol regulatory element binding proteins
T3: Triiodothyronine
T4: Thyroxine
TBT: Tributyltin
TCDD: 2,3,7,8-Tetrachlorodibenzodioxin
TCS: Triclosan
TDI: Tolerable daily intake
Tetra-PBDEs: Tetra-bromodiphenyl ethers
TGFβ: Transforming growth factor beta
TPhT: Triphenyltin
TWI: Tolerable weekly intake
WC: Waist Circumference
WHO-TEQ: WHO Toxic Equivalent

1. Introduction

Obesity is a complex multifactorial disease defined by excessive adiposity and it is associated with an increased risk of many non-communicable and communicable diseases such as COVID-19. The new report of the World Health Organisation (WHO) in Europe about obesity (WHO, 2022) indicates that obesity affects almost 60 % of adults and almost one in three children (29 % of boys and 27 % of girls). The document of the Organisation for Economic Co-Operation and Development (OECD), "The Heavy Burden of Obesity" (OECD, 2019), presents the prevalence data of overweight and obesity in 52 countries ranked from highest to lowest prevalence, with Spain in 7th place in obesity in adults and 4th place in child and adolescent population.

While improving dietary habits and increasing physical activity has been the main focus on reducing obesity, its rapid increase in countries with different dietary habits and physical activity patterns suggests the possible existence of environmental factors. In recent decades there has

been increasing research on the impact of environmental chemical pollutants called obesogens on the development of obesity. Obesogens have been defined functionally as chemical compounds that promote obesity by increasing the number of adipose cells and/or the accumulation of fat in existing adipocytes (Grün and Blumberg, 2006) (Janesick et al., 2014).

Because obesogens include a large number of compounds, exposure to them can occur by different routes such as inhalation, dermal exposure or ingestion, the latter being the main route of exposure. Obesogens are present in virtually all of the studied ecosystems and environments, having been identified in dust, water, food contaminants, food use containers, pesticides, cosmetics and personal care products, furniture and electronics, air pollution, solvents, disinfectants, sunscreens, plastics and plasticisers, artificial sweeteners, some antidepressants and antidiabetic drugs and common household products (Heindel et al., 2022).

Obesogens have diverse mechanisms of action and they can act by activating or antagonising the action of nuclear hormone receptors that directly regulate the expression of genes involved in the differentiation of adipocytes, body weight and metabolism, such as oestrogen receptors (ER), androgen and thyroid hormone, and the peroxisome proliferator-activated receptor-γ (PPARγ), among others. They can also act in the regulation of different immune-neuroendocrine metabolic pathways, which can lead to pathophysiological consequences in adipogenesis, lipogenesis, lipolysis, immunity, in the influence on the central regulations of appetite and energy expenditure, and changes in the intestinal microbiota, among other processes (Janesick et al., 2014) (Shahnazaryan et al., 2019) (Kladnicka et al., 2022).

It is important to highlight that the most critical periods of exposure to obesogens are preconception, pregnancy and childhood, given their importance for metabolism, and may result in permanent changes in adolescence and adulthood. Likewise, numerous obesogens have also been shown to have transgenerational effects (Lee and Blumberg, 2019).

The final effect of exposure to obesogens varies among individuals because it depends on the dose, route of exposure and co-occurrence of other environmental factors such as low socioeconomic status, stress, sleep disturbances, anxiety, depression, medications, hypercaloric diets, activity level, infections, microbiome, etc. Likewise, exposure is not limited to a compound but to a mixture of them. In addition, it should be noted that the obesogenic effect may vary depending on the stage of life in which the exposure occurs.

Considering that there are *in vitro* and *in vivo* data and epidemiological studies that support the existence of a relationship between exposure to these compounds and the incidence of overweight/obesity, and that, among other pathways, obesogens can be transported through food, a report of the current scientific evidence on the effects of dietary exposure to these compounds has been requested so that it can be considered by clinicians, regulatory bodies and the general population to reduce exposure and improve the social burden of this disease. In particular, the available scientific evidence of the effect of the most studied potentially obesogenic chemical compounds in the scientific literature and whose dietary exposure is high is presented. Figure 1 illustrates dietary exposure to obesogens.

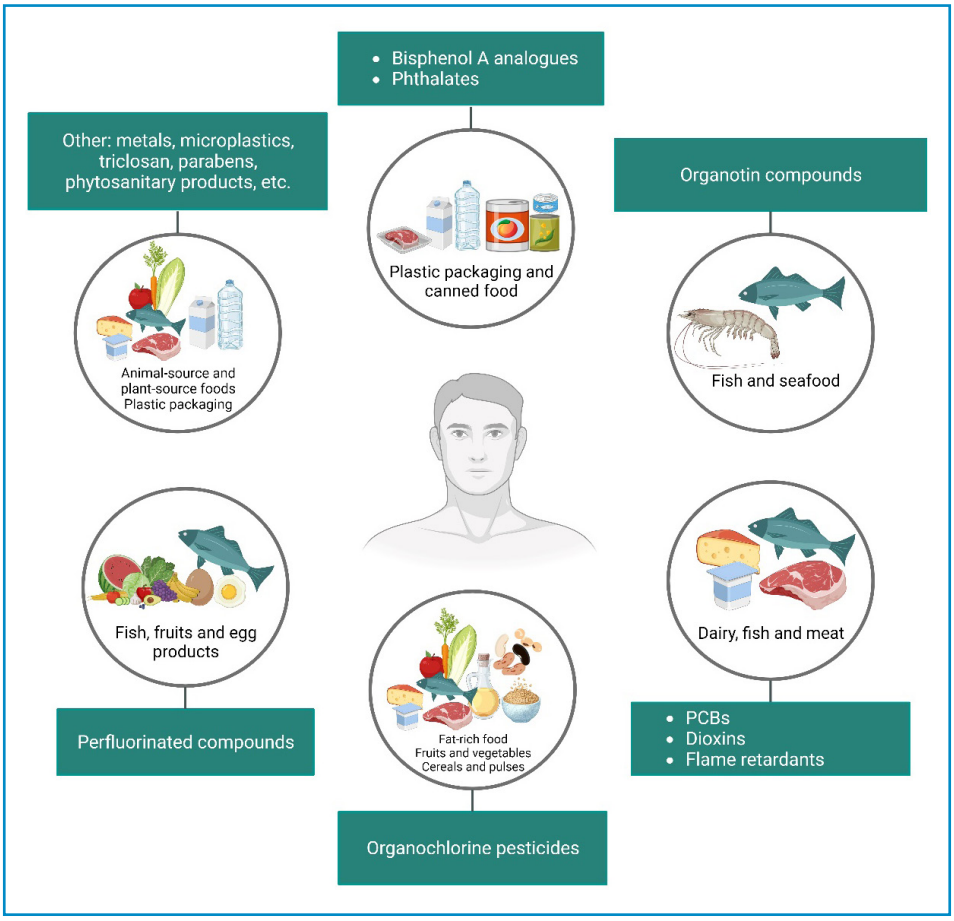

Figure 1. Food exposure to obesogens.

2. Bisphenol and analogues

2.1 Description and uses

Bisphenol A (BPA) and its analogues are produced in large quantities globally and their use has been increasing in recent decades. Due to this ubiquity, bisphenols have been detected in food, dust, sludge, drinking water, etc., with food being the main route of exposure to these compounds (Liu et al., 2018) (Martínez et al., 2020). Bisphenols are constituents of polycarbonate plastics and epoxy resins, which are used to make lacquers, varnishes, adhesives, plastics, water pipes, dental sealants, and food packaging. However, their presence in food packaging is not stable and they can migrate over time from the container to the food (Apau et al., 2018). Over the past years, the use of BPA has been regulated in different countries. Therefore, this compound is gradually being replaced by other bisphenolic compounds of similar structure that are being used as BPA alternatives in the industry. Among the most commonly used BPA analogues are bisphenol S (BPS), bisphenol F (BPF), bisphenol B (BPB), bisphenol E (BPE), and bisphenol AF (BPAF). Different experimental studies have

shown that BPA analogues have an obesogenic activity similar to this compound (Rochester and Bolden, 2015) (Boucher et al., 2016) (Darbre, 2017) (Verbanck et al., 2017) (Andújar et al., 2019).

2.2 Food exposure

While several studies determine the presence of BPA in food, few have analysed the presence of the analogues of BPA in food (Gálvez-Ontiveros et al., 2021). Canned and plastic packaged foods contain the highest amounts of BPA and analogues (Liao and Kannan, 2013) (González et al., 2020) (Gálvez-Ontiveros et al., 2021). However, bisphenols have also been detected in unpackaged foods, which could be due to contamination during primary production (Santonicola et al., 2019).

BPA is still the bisphenol most frequently detected in food in Europe (Cacho et al., 2012) (Cunha et al., 2012) (Fattore et al., 2015) (Česen et al., 2016) (González et al., 2020) (Gálvez-Ontiveros et al., 2021). Russo et al. (2019) reviewed data on the presence of BPA and analogues in European food, concluding that bisphenol concentration values are lower in northern than in southern Europe, with canned meat and vegetables being responsible for the highest dietary intakes of these compounds. In a study conducted in Spain (González et al., 2020), the exposure of the adult population to nine BPA analogues was evaluated through a duplicate diet study. BPA was detected in 93 % of canned and 36 % of non-canned foods, with a mean concentration of 22.49 µg/kg and 4.73 µg/kg, respectively. BPB was found in samples of olive oil and canned and non-canned chicken (mean concentration 2.40 µg/kg), and BPE in mushrooms and non-canned nuts (mean concentration 12.35 µg/kg). Dietary intake of BPA was estimated at 12.5 µg/day and 1.56 µg/day considering canned and non-canned foods, respectively. In the case of BPB, the dietary intake was similar for both groups, being 0.23 µg/day (canned) and 0.22 µg/day (non-canned). The estimated population intake of BPE was 0.14 µg/day and 0.58 µg/day in canned and non-canned food, respectively. The high presence of bisphenols in non-canned foods signals the ubiquity of these compounds along the food production chain, beyond packaging. A study conducted in Portugal (Barboza et al., 2020) investigated the presence of BPA and analogues in fish from the Atlantic Ocean. The estimated dietary exposure was 5.96 µg/kg body weight (b.w.)/day for BPA, 10.97 µg/kg b.w./day for BPB and 3.41 µg/kg b.w./day for BPE. Gálvez-Ontiveros et al. (2021) analysed BPA and analogues in 98 food samples in Spain. 52 % of the samples tested had detectable values of BPA and analogues, with BPA being the most frequently detected compound, followed by BPS and BPE. In addition, the estimated intake of bisphenols in children was 1.25 µg/kg b.w./day.

In 2015, the European Food Safety Authority (EFSA) reduced the Tolerable Daily Intake (TDI) of BPA from 50 to 4 µg/kg b.w./day. Currently, EFSA in its draft BPA re-evaluation has established a new TDI of 0.04 ng/kg b.w./day. This new TDI is exceeded by European consumers with average and high exposure to BPA (EFSA, 2021). At present, no TDI has been established for analogues.

2.3 Scientific evidence

In vitro and *in vivo* studies have demonstrated the obesogenic role of bisphenols. However, the limited number of epidemiological studies that have addressed the association between bisphenol exposure and obesity have shown conflicting results.

In vitro studies indicate that BPA, BPS and BPF promote adipocyte differentiation (Ahmed and Atlas, 2016) (Boucher et al., 2016) (Verbanck et al., 2017). In a study on adipose-derived stem cells (Adipose-Derived Stem Cells: ASCs) it was shown that BPA significantly increased adipogenesis, and this effect could be mediated through the oestrogen receptor pathway. The results of the molecular analysis showed that the expression of genes associated with adipogenesis was increased, like the PPARγ gene, among others (Ohlstein et al., 2014). In the 3T3-L1 murine cell model, BPA increased expression levels of the adipogenesis marker activator protein 2 (aP2), through an effect on the transcriptional activity of CCAAT/enhancer-binding protein δ (C/EBPδ) (Atlas et al., 2014). Boucher et al. (2014) noted that exposure to PBA-induced differentiation of primary preadipocytes through a non-classical RE pathway in the absence of exogenous glucocorticoids. In a study by Martinez et al. (2020), BPS followed by BPF showed a greater ability than BPA to increase lipid accumulation, which was reflected in the increased protein expression of PPARγ and fatty acid binding protein 4 (FABP4). Furthermore, in human mesenchymal stem cells (hMSCs) low doses of BPA and BPAF have significant effects on adipose cell development and lipid accumulation (Cohen et al., 2021) (Salehpour et al., 2021). Recently, Reina-Pérez et al. (2022) investigated the combined effect of BPA, BPS and BPF on adipogenic differentiation of human adipose-derived stem cells. Cells were exposed for 14 days to an equimolecular mixture of bisphenols (range 10nM-10mM) that promoted intracellular lipid accumulation in a dose-dependent manner and altered the expression of markers such as PPARγ, C/EBPα protein, lipoprotein lipase (LPL) and FABP4.

Furthermore, several studies on animals have found that exposure to BPA increases adipose tissue mass and promotes weight gain (Rubin et al., 2001) (Somm et al., 2009) (Rubin et al., 2017). The ability of BPA to inhibit adiponectin secretion in adipose tissue (Hugo et al., 2008), to alter plasma biochemical parameters, causing hypercholesterolaemia and hyperglycaemia (Marmugi et al., 2014), to increase body weight, fat tissue and leptin and insulin levels in the offspring of female mice exposed during pregnancy, and an increase in food intake in the latter has been described in animal models (Angle et al., 2013). In a recent review of *in vivo* studies looking at the effect of BPA on obesity, Naomi et al. (2022) concluded that BPA exposure increased adipogenesis, led to inflammation of adipose tissue, and alteration of lipid regulation producing transgenerational effects that could differ depending on the sex of the animal studied. The study by Desai et al. (2018) also shows how exposure to BPA during development caused weight gain in rodents (Virgin Sprague Dawley rats) due to increased food intake. This weight gain was associated with a reduced number of satiety neurons and an increased number of appetite neurons in the brain. BPA exposure during the pre and postnatal period through the maternal diet may also influence the melanocortin hypothalamic neurocircuit that controls feeding behaviour in CD-1 mice (Mackay et al., 2017). Stoker et al. (2020) conducted a study on male adult rats where they observed that perinatal exposure to BPA produced an alteration of glucose homoeostasis, induced obesity and increased food intake, altering hypothalamic signals, partially mimicking and/or producing an exacerbation of the effects of eating a high-fat diet. Another rodent study showed that prenatal exposure to low doses of BPA increased body weight associated with a three-fold increase in parametric white adipose tissue and adipocyte hypertrophy in female rats. Increased white adipose tissue was also associated with overexpres-

sion of lipogenic genes: PPARγ, C/EBPα, LPL, sterol regulatory element binding protein (SREBP), fatty acid synthase and stearoyl-CoA desaturase 1 (Somm et al., 2009).

Studies of the obesogenic effects of BPA analogues in animals are scarce compared to those of BPA. In a study by Ivry Del Moral et al. (2016) pregnant mice were exposed to BPS in water, and pups also received BPS through water from birth to 23 weeks of age. BPS induced overweight in mice, which was correlated with hyperleptinemia, hyperinsulinemia and total fat mass. However, the results were limited only to mice fed with a high-fat and BPS diet. The use of pregnant sheep shows that gestational exposure to BPA and BPS can affect preadipocytes but affects them differently depending on the compound. BPA specifically caused adipogenic differentiation in females, but not in males. Meanwhile, BPS caused similar differentiation, but only in males (Pu et al., 2017). In contrast, a study by Drobna et al. (2019) demonstrated that male mice fed with BPF gained less weight than the controls, but without effects on glucose levels or glucose tolerance. One mechanism of action that has been studied is the effect of exposure to BPA and its analogues on alterations in the synthesis and signalling of peripheral serotonin, especially in the intestine, which can contribute to obesity, since serotonin also plays a key role in the energy balance of mammals (Barra et al., 2022). The first study describing BPS as obesogenic at low doses during the perinatal period in male rodents showed a BPS-induced alteration in messenger ribonucleic acid (mRNA) expression from marker genes involved in adipose tissue homoeostasis (Ivry Del Moral et al., 2016).

In addition, several studies conducted on zebrafish (*Danio rerio*) showed how chronic exposure to PBA induced deregulation in genes related to lipid metabolism, causing hepatic steatosis (Martella et al., 2016) (Renaud et al., 2017) (Santangeli et al., 2018) (Sun et al., 2020). Chronic and acute exposure to PBA induced an alteration of the gene expression associated with hepatic metabolic disease by fatty deposition, indicating an alteration of lipid metabolism that could promote lipid accumulation in the liver and thus hepatic steatosis. Likewise, zebrafish exposure to BPF and BPS has been shown to cause alterations in metabolism including an alteration in triglyceride metabolism (Wang et al., 2018a) (Qiu et al., 2019) (Heindel et al., 2022).

Epidemiological studies on BPA and analogues focus mainly on BPA as an obesogen. Very few human studies have analysed the effect of analogues (Alharbi et al., 2022). Exposure to low doses of bisphenols has been associated with weight gain, altered carbohydrate and lipid homoeostasis, and an effect on brain regions involved in food intake (Boucher et al., 2016) (Verbanck et al., 2017) (Heindel and Blumberg, 2019). Kim et al. (2019), in a meta-analysis that included 13 studies analysing the effect of BPA on childhood obesity, showed that individuals highly exposed to BPA have a higher risk of developing obesity than those who are exposed to low levels of this compound (odds ratio (OR): 1.566, 95 % confidence interval (95 % CI): 1.097 to 2.234, p= 0.014). Ribeiro et al. (2020) conducted a meta-analysis to study the influence of endocrine disruptors exposure on anthropometric parameters concluding that there is a significant association between BPA exposure and overweight (OR: 1.254, 95 % CI: 1.005 to 1.564), obesity (OR: 1.503, 95 % CI: 1.273 to 1.774) and an increase in waist circumference (WC) (OR: 1.503, 95 % CI: 1.267 to 1.783) in adults.

A study published by Do et al. (2017), with 4733 adults aged 18-79, found that higher urinary BPA levels were positively associated with the risk of obesity (OR: 1.54 CI 95 % 1.00 to 2.37). These results

are consistent with other large-scale cross-sectional studies conducted in the United States (U.S.) and China. In a study derived from the National Health and Nutrition Examination Survey (NHANES) in the U.S., in a sample of 1500 adults aged ≥20 years, urinary levels of BPA, BPS, and BPF were associated with an increased risk of obesity even though the results were only significant for BPF. In another sample from NHANES (2013-2014) (Liu et al., 2019a), which includes 745 children and adolescents aged 6 to 17 years, the results showed a significant association between exposure to BPA and BPF with the development of general and abdominal obesity, after adjusting for demographic, socioeconomic and lifestyle factors and for urinary creatinine elimination. However, no relationship was found with BPS exposure. In another sample from the U.S. including 212 children from the Health Outcomes and Measures of the Environment (HOME) Follow-up Cohort (Gajjar et al., 2022) no positive association was observed between BPA exposure and Body Mass Index (BMI), percentage of body fat assessed by bioimpedance, anthropometry and dual-energy X-ray absorptiometry (DEXA), WC or adipocytokines (adiponectin/leptin).

Wang et al. (2012), in a study conducted in China, also found a positive association between urinary and serum BPA concentrations, and obesity in 3390 adults aged 40 years and older, together with a positive association between urinary BPA and abdominal obesity. Takeuchi et al. (2004) found higher serum BPA levels in Japanese women with polycystic ovary syndrome, regardless of their degree of obesity, and in obese women who did not have this syndrome. Another study showed that urinary BPA concentrations were higher in women with obesity and of ≥40 years (Milić et al., 2015). Finally, Zhao et al. (2012) demonstrated a statistically significant linear trend between fat mass and BPA exposure, as well as between serum leptin levels and BPA exposure, in 246 healthy premenopausal women.

Early exposure to bisphenols may have a greater effect and this may vary depending on sex. Braun et al. (2019) demonstrated that prenatal exposure to BPA was associated with an increase in central adiposity in girls aged 2 to 6 years and Hoepner et al. (2016) found an increase in body fat in 7-year-old girls, related to prenatal exposure to BPA, but not in boys. However, other studies do not confirm this association (Agay-Shay et al., 2015) (Buckley et al., 2016) (Vafeiadi et al., 2016) (Yang et al., 2017). Robles-Aguilera et al. (2021) demonstrated that overweight/obese girls showed an increased risk of high dietary exposure to BPA (OR: 3.38, 95 % CI: 1.25 to 9.07) and total bisphenols (OR: 2.81, 95 % CI: 1.03 to 7.67) compared to girls with a BMI of less than 25 kg/m^2. However, this effect was not observed in males. In a study by Liu et al. (2019a), BPA and BPF were shown to be more strongly associated with developing obesity in boys than in girls. Moon et al. (2022), in a work conducted within the Korean National Environmental Health Survey on more than 3000 adults aged 19 years and older, demonstrated that exposure to BPS has a greater association with the development of obesity in men than in women.

Table 1 shows a summary of the obesogenic effects of BPA and analogues demonstrated in the studies analysed in this report.

Table 1. Main findings of *in vitro*, *in vivo* and epidemiological studies on the obesogenic effects of bisphenols

Study type		Obesogenic effect	Reference
In vitro	- Murine 3T3-L1 preadipocytes - Primary human preadipocytes - Stem cells derived from human adipose tissue (adult mesenchymal stem cell)	- ↑ Adipogenesis, - ↑ Lipid accumulation	Ahmed and Atlas (2016); Boucher et al. (2016); Verbanck et al. (2017); Martínez et al. (2020); Cohen et al. (2021); Salehpour et al. (2021); Reina-Pérez et al. (2022)
In vivo	Rodents - CD-1 mice - Sprague-Dawley rats - c57BL/6 mice - rats derived from Wistar strain Sheep (Polypay Dorsett cross-multiparous and primiparous) Zebrafish (*Danio rerio*)	- ↑ Adipose tissue - ↑ Body weight, obesity - ↓ Adiponectin secretion - ↑ Leptin and insulin levels - ↓ Sensitivity to leptin - ↑ Appetite and ↓ satiety - ↑ Lipogenic genes - Hepatic steatosis - Hypercholesterolemia - Hyperglycaemia	Rubin et al. (2001); Somm et al. (2009); Angle et al. (2013); Marmugi et al. (2014); Ivry Del Moral et al. (2016); Martella et al. (2016); Mackay et al. (2017); Pu et al. (2017); Renaud et al. (2017); Rubin et al. (2017); Desai et al. (2018); Santangeli et al. (2018); Wang et al. (2018a); Drobna et al. (2019); Quiu et al. (2019); Stoker et al. (2020); Sun et al. (2020).
Epidemiological	Human	- ↑ Body weight - ↑ Body fat - ↑ Abdominal Obesity - General obesity	Takeuchi et al. (2004); Wang et al. (2012); Boucher et al. (2016); Hoepner et al. (2016); Do et al. (2017); Verbanck et al. (2017); Braun et al. (2019); Heindel and Blumberg (2019); Liu et al. (2019a); Zhao et al. (2021); Moon et al. (2022)

2.4 Summary of scientific evidence and comments

The studies analysed demonstrate that BPA and analogues stimulate adipocyte differentiation *in vitro*. BPA also affects the increase in body weight and adipose tissue in animal models. Several epidemiological studies available in the scientific literature have shown an association between BPA exposure and obesity in adults and children, as well as a relationship between prenatal exposure to these compounds and an obesogenic effect in offspring. However, other work in humans does not corroborate this data. In summary, the results of the studies demonstrate that there is scientific evidence that BPA acts as an obesogen, although more epidemiological studies are needed to confirm this effect. It is also necessary to investigate the obesogenic effect of BPA analogues since their presence in food is increasing because they are replacing BPA in food-use materials.

3. Phthalates

3.1 Description and uses

Phthalates are diesters of 1,2-benzenedicarboxylic acid that have high industrial production and are in a wide range of industrial and consumer products, including some plastic materials authorised to be in contact with food. They are colourless, odourless, and oily liquids that do not evaporate easily and do not chemically bind to the material to which they are added. Long chain phthalates such as diethylhexylphthalate (DEHP), diisononylphthalate (DiNP), diisodecylphthalate (DiDP), di-propylphenylphthalate (DPHP), butylbenzylphthalate (BBP) and di-n-octylphthalate (DOP) are used as plasticisers in hundreds of products made of polyvinyl chloride (PVC) plastic, mainly in plastic packaging and medical material. Low molecular weight short-chain phthalates such as dimethyl-phthalate (DMP), diethylphthalate (DEP), dibutylphthalate (DBP) and diisobutyliphthalate (DiBP) are widely used in many industries such as personal care and pharmaceutical (Wang and Qian, 2021).

3.2 Food exposure

One of the main ways people can be exposed to phthalates is through diet. Phthalates can be found in most products that come into contact with plastics during production, packaging or food delivery. For example, it has been shown that these chemicals can seep into food through vinyl plastic equipment and materials, food preparation gloves, and food packaging materials. Therefore, given the ubiquity of plastics, most people are exposed to some level of phthalates in the food field (Wang and Qian, 2021). For example, in China, the use of plastics tripled in 8 years, from 2003 to 2011, and reached more than 50 million tons of plastics produced, and it is estimated that it will continue to increase in the following years. As a result, due to the high use of plastic, relatively higher exposure to phthalates was found in China. In the U.S., more than 340 million pounds of phthalates are consumed annually, posing a potential risk to health and the environment (Wang and Qian, 2021). Indeed, metabolite biomarkers of eight major phthalates have been detected in 89 % to 98 % of the U.S. population (Serrano et al., 2014).

Serrano et al. (2014) conducted a review study considering 17 studies measuring phthalate concentrations in foods from different countries, describing food groups with high (≥300 µg/kg) and low (<50 µg/kg) concentrations, thereby estimating dietary intake. High concentrations of DEHP were consistently observed in poultry, cooking oils and cream-based dairy products (≥300 µg/kg) in all food follow-up studies. DPE was found in low concentrations in all food groups. Epidemiological studies showed a positive association between DEHP exposure and meat and dairy consumption. However, DEP was associated with vegetable intake. The estimated exposure to DEHP based on the American diet was 5.7, 8.1, and 42.1 µg/kg b.w./day for women of reproductive age, adolescents, and children, respectively, with dairy products contributing the most to this exposure. In addition, diets rich in meat and dairy were shown to increase exposure. Infant exposure exceeded the reference dose of 20 µg/kg b.w./day proposed by the U.S. Environmental Protection Agency (EPA).

In 2019, EFSA issued a scientific opinion on the risk assessment of the following phthalates: DBP, BBP, DEHP, DiNP and DIDP. The updated final assessment sets the group TDI at 50 µg/kg b.w./day, expressed as DEHP equivalents. For the DIDP, which is not included in this TDI, the estimated die-

tary exposure was always less than 0.1 µg/kg b.w./day. The highest exposure was found for DiNP, ranging from 0.2 to 4.3 µg/kg b.w./day, for an average consumer. However, EFSA warns that all these TDIs have been set temporarily due to uncertainties about the effects other than the reproductive, and the contribution of plastic food contact materials to consumers' overall exposure to phthalates (EFSA, 2019). Therefore, exposure to a greater or lesser extent in the food chain of consumption is inevitable. People are exposed to phthalates by eating and drinking foods that have come into contact with products containing these compounds. Also, some exposure may occur when breathing airborne phthalate particles. In addition, children crawl and touch things, and then put their hands in their mouths. Because of this hand-to-mouth behaviour, the phthalate particles in dust may pose a greater risk to children than to adults.

3.3 Scientific evidence

Existing data demonstrate the adipogenic potential of phthalate exposure due to the up-regulation of PPARγ produced by mono-2-ethylhexylphthalate (MEHP), DEHP, monobenzylphthalate (MBzP), monosecbutylphthalate, benzylbutylphthalate and DiNP (Hurst and Waxman, 2003) (Feige et al., 2007) (Desvergne et al., 2009) (Yin et al., 2016) (Sakuma et al., 2017) (Zhang et al., 2019a). Another mechanism of promotion of adipogenesis is through the regulation and activation of C/EBPα expression, as has been demonstrated in pluripotent stromal cells of the bone marrow (Hao et al., 2021). Likewise, exposure to phthalates induces adipogenesis in 3T3L1 cells by activating the corticosteroid receptor (Sargis et al., 2010) (Singh et al., 2020). It has been reported that phthalates interfere with the secretion of adipokines. DEHP and MEHP cause a decrease in leptin mRNA expression and a decrease in adiponectin secretion (Schmidt et al., 2012) (Chiang et al., 2017). Finally, exposure to phthalates has been associated with alterations in the regulation of lipid metabolism which induce an accumulation in adipocytes and dysfunction and inflammation of the adipose tissue. (Aaseth et al., 2022). Therefore, exposure to phthalates promotes adipogenesis by activating C/EBPα and PPARγ signalling, as well as lipid accumulation in adipocytes due to activation of lipid biosynthesis. In addition, adipokine deregulation, adipose tissue inflammation, and epigenetic effects induced by phthalate exposure may also contribute to obesity and associated metabolic alterations (Aaseth et al., 2022).

In a systematic review that included 31 studies on the effect of early DEHP exposure on obesity, the authors conclude that exposure is associated with an increase in rodent adiposity (Wassenaar and Legler, 2017). Likewise, in rodents, prenatal exposure to low doses of DEHP (0.2 mg/kg b.w./day) resulted in metabolic syndrome, which includes abnormal adipogenesis, energy expenditure, and glucose metabolism, along with dysbiosis of the intestine microbiome, in male offspring. In particular, the hepatic metabolism of thiamine was disrupted in these offspring due to the deregulation of thiamine transporter enzymes, resulting in abnormal glucose metabolism (Fan et al., 2020). A recent study has shown that chronic DEHP exposure in mice induces obesity through disruption of the lipid metabolism and an alteration of the intestine microbiota (Su et al., 2022). Different studies in zebrafish have demonstrated an obesogenic effect of phthalates through different mechanisms such as modulation of the expression of liver genes related to fatty acid metabolism, and lipid accu-

mulation in hepatocytes, resulting in oxidative stress and alteration of the microbiota, among other demonstrated mechanisms (Chen et al., 2016) (Zhang et al., 2017, 2019b) (Jacobs et al., 2018) (Huff et al., 2019) (Buerger et al., 2019, 2020).

Regarding epidemiological studies, an experimental phthalate exposure study conducted between 2017 and 2020 on a cohort of 2298 children between 7 and 13 years old in China, showed that exposure to these compounds during childhood could significantly increase the risk of overweight and obesity, with a dose-response relationship, especially in girls (Dong et al., 2022). Another study conducted on 1269 individuals exposed to a combined exposure of phthalates, two pesticides and two phenols concluded that 38.5 % had general obesity and 58.0 % had abdominal obesity, being mono (carboxyl) phthalate (MCOP) was one of the factors associated with it (Zhang et al., 2019a).

A 2014 review highlighted that 26 epidemiological studies prior to this date found no inter- or intra-study consistency for an association between the presence of serum or urine phthalate metabolites and indicators of overweight/obesity in children or adults (Goodman et al., 2014). However, several other studies have been published linking the presence of phthalates in the human body and the risk of obesity, with a large sample size (128-3752 subjects) that evaluated three types of phthalates, DEP, DEHP and benzylphthalate (BzBP) (Hatch et al., 2008) (Teitelbaum et al., 2012) (Kim et al., 2016) (Amin et al., 2018) (Mansouri et al., 2019) (Lim et al., 2020). Four of these studies have shown a positive relationship between exposure to phthalates and obesity. In a very recent literature review, Lee et al. (2022) studied whether prenatal or postnatal exposure to phthalates is associated with physical growth disorders in children. The authors conclude that prenatal exposure to phthalates is associated with a decrease in BMI in children but is not related to body fat percentage. These findings suggest that phthalates may disrupt children's normal muscle development, rather than inducing obesity, as had been raised in other studies (Lee et al., 2022). Therefore, from an epidemiological point of view, although some studies show a relationship between phthalate exposure and obesity, it is still unclear and more prospective studies confirming this trend are needed (Aaseth et al., 2022).

Table 2 shows a summary of the obesogenic effects of phthalates demonstrated in the studies analysed in this report.

Table 2. Main findings of *in vitro*, *in vivo* and epidemiological studies on the obesogenic effects of phthalates

Study type		Obesogenic effect	Reference
In vitro	- COS cells - Liver cells (PPARalpha) - Adipocyte cells (PPARgamma) sensitive to PPAR - Pluripotent bone marrow stromal cells - COS7, C2C12, HeLa and 3T3L1 cells - Hepatocytes BRL-3A	- ↑ Adipogenesis - ↑ Lipid accumulation - Deregulation of adipokines - ↓ Leptin mRNAexpression - ↓ Adiponectin secretion - Dysfunction and inflammation of adipose tissue	Hurst and Waxman (2003); Feige et al. (2007); Desvergne et al. (2009); Yin et al. (2016); Sakuma et al. (2017); Zhang et al. (2019a); Sargis et al. (2010); Singh et al. (2020); Schmidt et al. (2012); Chiang et al. (2017); Aaseth et al. (2022)
In vivo	Rodents - CD-1 Mice - C57BL/6J mice - ICR mice - Sprague-Dawley rats - Wistar Rats Zebrafish (*Danio rerio*)	- ↑ Adiposity - ↑ Adipogenesis - Disruption of lipid metabolism - Alteration of the intestinal microbiota - Impaired glucose metabolism - Modulation of liver gene expression - Lipid accumulation in hepatic cells - ↑ Oxidative stress	Fan et al. (2020); Su et al. (2022); Chen et al. (2016); Zhang et al. (2017); Jacobs et al. (2018); Huff et al. (2019); Buerger et al. (2019, 2020)
Epidemiological	Human	- ↑ Risk of overweight and general obesity - ↑ Abdominal Obesity - ↓ BMI and impaired muscle development	Dong et al. (2022); Zhang et al. (2019b); Goodman et al. (2014); Hatch et al. (2008); Teitelbaum et al. (2012); Kim et al. (2016); Amin et al. (2018); Mansouri et al. (2019); Lim et al. (2020); Lee et al. (2022); Aaseth et al. (2022)

3.4 Summary of scientific evidence and comments

The results of the *in vitro* and *in vivo* studies show a direct relationship between exposure to phthalates, especially DEHP, and the promotion of adipogenesis by lipid accumulation in adipocytes, thus, contributing to obesity and the associated metabolic alterations. Epidemiological studies expose controversial results. However, due to the presence of phthalates in numerous products in contact with food, it is recommended to reduce as far as possible the use of these substances in the manufacture of these materials, also decreasing the use of plastics to minimise the exposure of consumers to them.

4. Organotin compounds (OTs)

4.1 Description and uses

Organotin compounds (OTs) have a wide variety of uses, including their use as stabilisers in plastics; defoamers in paints; wood preservatives and pesticides; and anti-fouling paints for ships (Chen et al., 2019) (He et al., 2020) (Sadighara et al., 2021). The wide use of OTs has resulted in many of them

having passed into the food chain, accumulating in various ecosystems. Of particular interest is the case of tributyltin (TBT), due to its genotoxic effects on aquatic populations, even at very low doses (<1 ng/l) (Amodio-Cocchieri et al., 2000) (Santos et al., 2009).

4.2 Food exposure

These products have been found in ocean sediments and seawater from ports around the world, including Europe, Asia and North America (Ashraf et al., 2017) (Zhan et al., 2020). It is estimated that the average accumulated TBT in seafood from all global coasts can reach 182.33 ng/g (Mattos et al., 2017) (Sadighara et al., 2021). In Italy, 33 % of the fish in the sea and 85 % of those that came from fish farms were contaminated with OTs (Amodio-Cocchieri et al., 2000). TBT and triphenyltin (TPhT) have also been detected in household dust and soil materials in Germany, the Netherlands, United Kingdom and U.S. (Fromme et al., 2005) (Kannan et al., 2010).

EFSA states that the TDI for the four main OT compounds, TBT, TPhT, dibutyltin (DBT) and di-n-octyltin (DOT) should be a maximum of 0.25 µg/kg b.w./day (Chung et al., 2020). However, these products can bioaccumulate in tissues, favouring their toxicity over the long term. Bioaccumulation of OTs has been seen in blood from populations in the U.S. and it has been associated with immune dysfunctions (Inadera and Shimomura, 2005). Likewise, the presence of TBT in the liver has been detected in very distant populations in the balloon in the range of 11 to 96 ng/g wet weight (Rantakokko et al., 2014).

4.3 Scientific evidence

In vitro studies show that OT compounds promote adipocyte differentiation as PPARγ/retinoid X receptor (RXR) pathway agonists (Kanayama et al., 2005) (Grun and Blumberg, 2006) (Grun et al., 2014). TBT activates the three heterodimers RXR-PPARα, -γ, -Δ, mainly through its interaction with RXR, TBT binds to RXR as a covalent adduct to cysteine 432 of helix 11 of the RXRα protein (Le Maire et al., 2009). Inadera and Shimomura (2005) investigated the effect of TBT on adipocyte differentiation. When confluent 3T3-L1 cells were incubated with TBT for 2 days in the presence or absence of isobutylmethylxanthine, dexamethasone and insulin, lipid accumulation in adipocytes increased considerably. Another study shows that TBT can activate the RXR-PPARγ heterodimer, inducing adipogenesis, triglyceride storage and expression of adipogenic marker genes in 3T3-L1 cells in a PPARγ-dependent manner (Li et al., 2011). Likewise, Kirchner et al. (2010) observed that TBT exposure alters the stem cell compartment by sensitising multipotent stromal stem cells to differentiate into adipocytes, an effect that could likely increase adipose mass over time. Other results show that TBT shifted the differentiation of bone marrow-derived mesenchymal cells and adipose tissue preferentially to the adipose lineage and away from the bone lineage in exposed mice (Yanik et al., 2011). In addition, TBT has been found to promote both RXRα protein turnover and lipid accumulation, because this compound, in a time- and dose-dependent manner, significantly reduced RXRα levels (Stossi et al., 2019).

In animal models (Zhan et al., 2020), TBT exposure in food induces a significant increase in body weight and epididymal fat, as well as adipocyte hypertrophy, directly related to obesity (Ouadah-Boussouf and Babin, 2016) (Murphy et al., 2017). High lipid levels may aggravate the inflammatory response (Miglio et al., 2013) (Manzoni et al., 2019), which may be associated with elevated pro-inflammatory cytokines in the adipose tissue of obese animals.

TBT can alter thyroid hormone functions through down-regulation of thyroid peroxidase and suppression of T4 (thyroxine) and T3 (triiodothyronine) levels (Sharan et al., 2014). Thyroid hormones play a critical role in the homoeostasis of glucose metabolism through the promotion of islet maturation and the maintenance of normal physiological function of pancreatic alpha and beta cells (Matsuda et al., 2017). Therefore, decreasing the level of T4 and T3 may promote the development of dysbiosis of glucose and insulin homoeostasis in mice.

On the other hand, TBT exposure significantly decreases testosterone concentration in mice. This hormone is capable of reducing fat accumulation, inhibiting the inflammatory response and promoting liver fat oxidation in male mammals (Markle et al., 2013) (Pintana et al., 2015). Therefore, the lack of T3, T4, and testosterone induced by TBT exposure may contribute to impaired glucose and insulin homoeostasis and overweight in animal models.

Meanwhile, in-uterus exposure to TBT resulted in an apparently high accumulation of lipids in the adipose deposits, liver and testes of neonatal mice and an increase in epididymal adipose mass in adult mice (Grün et al., 2006). In addition, TBT has been shown to disrupt endocrine signalling, interacting with the oestrogen receptors ERα and ERβ, the RXR and the PPARg, which potentially promote adipogenesis in mice (Grün et al., 2006) (Penza et al., 2011).

Epidemiological studies on the relationship between exposure to organotin compounds and obesity are very scarce. To the best of our knowledge, there is only one prospective Finnish study linking exposure to OTs compounds to obesity. In this work, 110 samples of human placenta were collected and the presence of TBT, DBT and TPhT was analysed. TBT was detected in 99 % of placentas above the limit of quantification. However, for the remaining OTs compounds, the detected concentrations were below the limit of quantification in 90 % (DBT) and 57 % (TPhT) of the samples. The results showed that TBT detected in placenta was positively associated with weight gain during the first three months of life (Rantakokko et al., 2014). However, no association was found between the presence of placental OTs and the weight of children at a later age.

Table 3 shows a summary of the obesogenic effects of organotin compounds demonstrated in the studies discussed in this report.

Table 3. Main findings of *in vitro*, *in vivo* and epidemiological studies on the obesogenic effects of OTs

Study type		Obesogenic effect	Reference
In vitro	- Murine 3T3-L1 preadipocytes - Primary human preadipocytes - Stem cells derived from human adipose tissue (adult mesenchymal stem cell)	- ↑ Adipogenesis - ↑ Lipid accumulation	Kanayama et al. (2005); Inadera and Shimomura (2005); Grun and Blumberg (2006); Kirchner et al. (2010); Li et al. (2011); Yanik et al. (2011); Grün et al. (2014); Stossi et al. (2019)
In vivo	Rodents - CD-1 mice - Sprague-Dawley rats - c57BL/6 mice - Rats derived from Wistar strain Sheep (Polypay Dorsett cross-multiparous and primiparous) Zebrafish (*Danio rerio*)	- ↑ Adipose tissue - ↑ Body weight, obesity - ↑ Inflammatory Response - ↓ Testosterone - Alteration of thyroid hormones - Glucose homoeostatic dysbiosis	Markle et al. (2013); Pintana et al. (2015); Sharan et al. (2014); Murphy et al. (2016); Ouadah-Boussouf and Babin (2016); Matsuda et al. (2017); Zhan et al. (2020)
Epidemiological	Human	- ↑ Body weight at 3 months of age - Presence in placentas	Rantakokko et al. (2014)

4.4 Summary of scientific evidence and comments

The enormous toxicity of organotin compounds, as well as their persistence, makes it necessary to study their consequences on human health. The obesogenic effect of TBT has been extensively demonstrated both *in vitro* and *in vivo* studies. However, epidemiological studies have been scarce.

Given the demonstrated obesogenic effect of this compound in cell and animal models, further epidemiological studies are needed to analyse the effect of exposure to this compound on obesity and other associated pathologies.

5. Polychlorinated biphenyls (PCBs)

5.1 Description and uses

Polychlorinated biphenyls (PCBs) are known persistent organic pollutants that were widely used as cooling fluids in a wide range of electrical and electronic devices (Madgett et al., 2022). They were also used as paint additives, in carbonless copying paper and plastics, in addition to being unintentionally produced during combustion (Lee et al., 2014). PCBs have been banned in the U.S. since 1979 and in Europe since 1987 (Madgett et al., 2022). This prohibition acquired an international character in the Stockholm Convention of the United Nations on May 23, 2001, with 184 countries having currently ratified the convention (Mishra et al., 2022). Despite its prohibition, there is still an unintended emission in some industries such as the production of silicone rubber (Hombrecher

et al., 2021). This, together with their high persistence, means that exposure to these compounds remains high, especially through diet (Heindel et al., 2022).

PCBs can lead to cancer, genetic defects, DNA damage, dermal issues, and various alterations related to the liver, kidney, and heart (Christensen et al., 2021). In addition, they are classified as endocrine disruptors with the ability to produce obesogenic effects in humans since they mimic, antagonise or modify natural hormonal activity (Domazet et al., 2020). There are 209 congeners, of which endocrine disrupting action has been observed in both oestrogenic (PCB-44, PCB-49, PCB-52, PCB-101, PCB-187) and antiestrogenic (PCB-64, PCB-74, PCB-77, PCB-105, PCB-118, PCB-128, PCB-138, PCB-170).

5.2 Food exposure

The main contribution to PCBs in the diet is from foods of animal origin, mainly those with fat content, having found the highest levels of PCBs in adipose tissue, both animal and human (Dewailly et al., 1999) (Kania-Korwel et al., 2005) (Covaci et al., 2008). Foods such as milk and its derivatives (butter and cheese), fish and livestock meat should be highlighted (Yu et al., 2021).

EFSA's Panel on Contaminants in the Food Chain (Panel CONTAM) established a Tolerable Weekly Intake (TWI) of 2 pg TEQ/kg b.w./week for dioxins and dioxin-like PCBs (EFSA, 2018). This scientific opinion states that, based on European consumption data and the presence of these compounds in food, in the adolescent, adult and elderly age groups, the TWI is considerably exceeded.

5.3 Scientific evidence

The interaction with the aryl hydrocarbon (AhR) receptor has been described as a mechanism of the obesogenic action of PCBs. Other obesogenic mechanisms have also been described, such as the pathway of the nuclear enhancer factor for kappa light chains of activated B cells (NFkB) (Wu et al., 2017) and of the Fsp27 protein (Kim et al., 2017). The obesogenic effect of PCBs is congener-specific and there is much left to be studied (Veiga-Lopez et al., 2018).

Overall, PCBs appear to be involved in adipogenesis regulation; however, while PCB-126 (dioxin-like) has an inhibitory effect on adipogenesis (Brodie et al., 1997) (Gadupudi et al., 2015) that is possibly dependent on a molecular mechanism activating the AhR receptor (Hanlon et al., 2003), those that do not behave like dioxin (PCB-153 and -138) have an adipogenic effect in murine cells differentiated into adipocytes 3T3L-1 and in Human Preadipocytes-visceral (HPA-v) cell lines (Sales et al., 2013) (Kim et al., 2017) (Yu et al., 2021). In addition, this adipogenic effect has also been demonstrated *in vivo* in female mice exposed to PCB-153 with an increase in body fat, an increase in the size of subcutaneous abdominal adipocytes and a build-up of lipids in the liver and dyslipidemia (Chi et al., 2018) (Min et al., 2020). These studies linked these effects with the alteration of the intestinal microbiota.

Different epidemiological studies have revealed a relationship between PCBs exposure and a higher prevalence of obesity (Donat-Vargas et al., 2014) (Lauritzen et al., 2018) (Leong et al., 2019) (Wolf et al., 2019). However, such an association between the presence of PCBs and the described adverse effects has not always been detected. A positive relationship between dietary PCB intake

and increased incidence of obesity has been observed in a prospective study in Spain on more than 12 000 individuals (Donat-Vargas et al., 2014). Also in Spain, an association was found between increased BMI and exposure to PCB-138 and PCB-180 (Agay-Shay et al., 2015). Exposure to low levels of PCB-153 has been associated with low weight in neonates in a European study on 7990 individuals (Govarts et al., 2012). Notably, low birth weight is associated with an increased risk of obesity in adolescence and adulthood (Jornayvaz et al., 2016) (Martín-Calvo et al., 2022). In contrast, a study on 145 individuals observed a negative relationship between serum levels of PCB-153, PCB-180, and PCB-170 and BMI and adipose tissue (Dirinck et al., 2011). Similarly, recent studies point out that PCBs body burden is not related to the increased prevalence of obesity in an Indigenous population in Canada (Akbar et al., 2021).

Another key aspect is prenatal exposure. There is epidemiological evidence that PCBs can cross the placental barrier and reach the foetal circulation at 50 % of that observed in the maternal circulation (Soechitram et al., 2004) (Park et al., 2008). It has been shown that the exposure of parents before conception to PCBs can influence the weight of the neonate (Robledo et al., 2015). Exposure of infants through breast milk is important, although in a study conducted on milk from mothers with obesity and normal weight, no significant differences in the presence of PCBs were observed between both groups (Gautam et al., 2020). It is also important to note that PCBs that accumulate in adipose tissue can be released into the systemic circulation during weight loss (Louis et al., 2014).

Table 4 shows a summary of the obesogenic effects of PCBs demonstrated in the studies analysed in this report.

Table 4. Main findings of *in vitro, in vivo* and epidemiological studies on the obesogenic effects of PCBs

Study type		Obesogenic effect	Reference
In vitro	- 3T3-L1 (preadipocytes) - AML-12 (hepatocytes)	- ↑ Triglycerides - ↑ Adipose tissue - ↓ Glucose absorption - Fat-specific protein-mediated insulin resistance 27	Wu et al. (2017); Kim et al. (2017)
In vivo	Rodents - C57BL/6 female mice	- ↑ Abdominal adipose tissue - Lipid accumulation in the liver - ↑ Expression of pro-inflammatory cytokines (TNF-a, iNOS and IL-6)	Chi et al. (2018); Min et al. (2020)
Epidemiological	Human	- ↑ BMI - ↑ Adipose tissue - ↓ Weight in neonates - Not related to obesity	Donat-Vargas et al. (2014); Lauritzen et al. (2018); Leong et al. (2019); Wolf et al. (2019); Agay-Shay et al. (2015); Govarts et al. (2012); Dirinck et al. (2011); Akbar et al. (2021)

5.4 Summary of scientific evidence and comments

Available *in vitro*, *in vivo* and epidemiological studies indicate a possible obesogenic effect of these compounds. However, their study is extremely complex, due to the wide variety of existing congeners, since in some cases the opposite obesogenic effects have been confirmed, also existing dose dependence. On the other hand, the population is frequently exposed to a mixture of PCBs, making it even more difficult to study the relationship between exposure to these compounds and obesity. More work is needed to study the obesogenic effect of PCBs, considering the combined effect with other persistent organic compounds such as dioxins that have similar mechanisms of action.

6. Dioxins

6.1 Description and uses

The term dioxin comprises the polychlorinated dibenzodioxins (PCDDs) which are a family of 75 congeners and the polychlorinated dibenzofurans (PCDFs) which are 135 (Lee et al., 2014). These compounds are produced unintentionally except for research purposes. They can be produced as undesirable by-products of certain processes such as the manufacture of other chemicals or bleaching in paper mills; they are also released from incinerators and formed during chlorination in wastewater and drinking water treatment plants (Lee et al., 2014). They are included in the list of persistent organic pollutants of the United Nations Stockholm Convention. Of these, 2,3,7,8-tetrachlorodibenzodioxin (TCDD) stands out as the most toxic and studied dioxin, being classified by the International Agency for Research on Cancer (IARC) as carcinogenic to humans (Heindel et al., 2022).

6.2 Food exposure

A review conducted between 2010 and 2021, using data from different countries indicated that, despite the presence of these compounds in different foods, the tolerable daily/weekly/monthly dietary intakes of polybrominated dibenzo-p-dioxins and furans are currently not exceeded in most cases (González and Domingo, 2021). They also point out that the values of these contaminants have decreased in both food and humans and that, based on data allowing comparison over time, a very significant reduction has been observed from 210 pg I-TEQ/day in 1998 to 8.54 pg WHO-TEQ/day in 2018 (González et al., 2018), this reduction being parallel to blood values in humans (Nadal et al., 2019). However, other recent studies state that, despite this decrease in the levels of these pollutants, there are subgroups of the population, such as children, that exceed the tolerable intake of 2 pg TEQ/kg b.w./week from the consumption of contaminated food in Italy (Ceci et al., 2022).

Dibenzodioxins and polychlorinated dibenzofurans are found in foods of animal origin such as meat, fish, milk and eggs (Rusin et al., 2019), with food being the main route of exposure for the general population (González and Domingo, 2021). WHO established a TDI of 10 pg/kg b.w./day for TCDD, considering its hepatotoxic, immunotoxic and reproductive effects in experimental animals (WHO, 1991). In 1998, the TDI was modified to 1-4 pg TEQ/kg b.w./day (WHO, 1998). Subsequently, different guide values have been established: TWI of 14 pg WHO-TEQ/kg b.w./week (SCF, 2001) and a tolerable provisional monthly intake of 70 pg TEQ/kg b.w./month (JECFA, 2001). Nevertheless, the

reference value in the U.S. is more conservative, having proposed an oral Reference Dose (RfD) of 0.7 pg/kg b.w./day, three times lower than the value in Europe (EPA, 2012). In 2018, EFSA's CONTAM Panel completes this comprehensive review, considering new epidemiological resources for observing human effects and animal test data as supporting evidence, as well as more refined pharmacokinetic modelling techniques. In conclusion, the Panel established a new TWI for dioxins and dioxin-like PCBs in foods of 2 pg/kg b.w., seven times lower than the previous value (EFSA, 2018).

6.3 Scientific evidence

The mechanism of obesogenesis of these compounds appears to be due to their agonism with the AhR receptor. TCDD is known to exhibit antiadipogenic effects with decreased expression of C/EBPβ, PPARγ2, key adipogenic factors (aP2) and glucose transporter type 4 (GLUT4). It also causes decreased glucose uptake or LPL activity in 3T3-L1 cells, C3H10T1/2 cells and rat primary adipocytes (Brodie et al., 1997) (Nagashima and Matsumura, 2002) (Cimafranca et al., 2004). In experimental animals, alterations in serum triglyceride concentrations and liver damage have been observed, these being more severe in mice fed a high-fat diet (Duval et al., 2017). Similar results were observed in female mice exposed to TCDD during lactation and pregnancy, with increased susceptibility to high-fat diet-induced obesity and diabetes (Hoyeck et al., 2020). Likewise, it was confirmed that TCDD dioxin is also obesogenic in adult mice fed a high-fat diet (Brulport et al., 2017). Therefore, we can say that TCDD influences obesity in *vivo* depending on the doses used and the type of diet (La Merrill et al., 2009). Also mention that, like PCBs, it has been seen that TCDD can alter both microbiome composition and host-microbiota interactions (Brawner et al., 2019).

Although it was not an oral presentation, it is worth mentioning the incidents of the Vietnam War (spraying with a TCDD herbicide over Vietnam between 1962 and 1971) (Longnecker and Michalek, 2000) and the explosion of a chemical factory in Seveso, Italy, in 1976 (Eskenazi et al., 2018). These incidents allowed the collection of epidemiological data from cohorts with accidental exposure (Vietnam War veterans and residents near Seveso) or work (farmers) exposed to high doses of dioxin, leading to an increased risk of diabetes and impaired glucose metabolism and insulin signalling (Taylor et al., 2013) (Goodman et al., 2015) (Eskenazi et al., 2018) in line with the data from rodent studies. However, there is no clear data associating exposure to TCDD with an increased risk of obesity (Heindel et al., 2022).

A study conducted in China observed that blood concentrations of PCDD/Fs found in women were higher than in men in all age groups (Han et al., 2022). These studies also found that concentrations of PCDD/Fs and PCBs in women's blood were 6.6 to 37 times higher than in umbilical cord blood, and that it was more evident in compounds with higher chlorine content, which likely have greater difficulty crossing the placental barrier.

Table 5 shows a summary of the obesogenic effects of dioxins demonstrated in the studies analysed in this report.

Table 5. Main findings of *in vitro*, *in vivo* and epidemiological studies on the obesogenic effects of dioxins

Study type		Obesogenic effect	Reference
In vitro	Preadipocytes derived from epididymal cells - 3T3-L1 cells - C3H10T1/2 cells	- ↓ mRNA for C/EBPα - ↓ mRNA for PRARγ2 - ↓ mRNA for PRARγ - ↓ mRNA for aP2 - ↓ Glucose uptake - ↓ Size and number of lipid vesicles within adipocytes	Brodie et al. (1997); Nagashima and Matsumura (2002); Cimafranca et al. (2004)
In vivo	Rodents - C57BL/6J mice - C57BL/6 mice - DBA/2J mice	- ↑ Hepatic impairment - ↑ Cyp1a1 expression - ↑ Body weight, obesity in females - ↓ Leptin in female sex - ↑ Fasting blood glucose - ↑ Adipose tissue	Duval et al. (2017); Hoyeck et al. (2020); Brulport et al. (2017); La Merrill et al. (2009)
Epidemiological	Human	- Higher blood concentrations in females - ↑ Increased risk of diabetes in people with high levels of dioxins in the blood	Han et al. (2022); Longnecker and Michalek (2000)

6.4 Summary of scientific evidence and comments

The studies available so far both in humans and rodents, even *in vitro*, cannot establish a clear relationship between PCDD/Fs exposure and obesogenic effect. In some cases, this effect has been observed under certain circumstances, highlighting the presence of other compounds that possibly act synergistically. As in the case of PCBs, what has been demonstrated is their participation in other obesity-related pathologies, such as inflammation and metabolic alterations. Further studies are needed to investigate the obesogenic effect of dioxins, considering their interaction with other persistent organic compounds that act with similar mechanisms of action.

7. Organochlorine pesticides

7.1 Description and uses

Different classes of organochlorine pesticides have been studied for their obesogenic capacity, the most widely examined being dichlorodiphenyltrichloroethane (DDT) and its metabolite dichlorodiphenyldichloroethylene (DDE) which is highly lipophilic and persistent in the environment and in the food chain.

Organochlorine pesticides have been banned in most countries, but due to their residual character and accumulation in the food chain, as they are ubiquitous and persistent compounds, they have been detected in air, water, marine sediments, as well as in fish and wildlife (Zumbado et al., 2004) (Keswani et al., 2022).

7.2 Food exposure

Organochlorines have high persistence in the environment (from months to years) (Yang et al., 2017), causing harmful effects on humans, both acute and chronic, depending on the amount and mode of exposure. Exposure to these chemicals is widespread worldwide through pollution of air, water, food, and many consumer goods, including plastics and cosmetics. Because of their semi-volatile nature, they can travel a great distance, carried by the wind. Moreover, being lipophilic molecules, they have a great capacity to accumulate through the trophic chain, mainly in the adipose tissue of organisms (Rosenfeld and Feng, 2011). Therefore, they are most commonly detected in high-fat foods. We can ingest them through fatty fish and meats, milk and derivatives (Linares et al., 2010). However, crops may be contaminated, so fruits, vegetables, oils, grains, and legumes may also be sources of organochlorine pesticides (Guo et al., 2019).

The report prepared by EFSA (Chemicals in food) (EFSA, 2016a) indicates that, for the 12 products analysed in that report, the probability of European citizens being exposed to concentrations of pesticide residues that may pose a health risk is low in the short term, and negligible in the long term. Member States and the European Commission lay down rules on pesticide risk management such as the establishment of legal limits for pesticide residues in food and feed (Maximum Residue Limits or MRLs).

7.3 Scientific Evidence

Studies in cell cultures with pre-adipocytes have shown that organochlorine pesticides exert an obesogenic effect through the activation of adipogenesis. This is due to their ability to activate transcription factors that regulate this process, such as PPARγ. Using the murine cell line of pre-adipocytes 3T3-L1, it has been observed that cells exposed to DDT cause the overexpression of this transcription factor as well as the sterol-1c regulatory element binding proteins (SREBP-1c) and C/EBP-1α, which are also factors that regulate adipogenesis (Moreno-Aliaga and Matsumura, 2002). Increased cell proliferation has also been observed in human mesenchymal cells, with increased expression of genes such as PPARγ, the glucose transporter GLUT4, and the LPL enzyme (Strong et al., 2015).

Studies in rodents have shown that the effects of DDT on adiposity may also be related to a reduction in thermogenesis and, therefore, in energy expenditure (La Merrill et al., 2014). Thus, in this study, the administration of DDT to mice during pregnancy produced a reduction in body temperature, cold tolerance and energy expenditure, and a transient increase in body fat, in the female offspring when they reached the adult stage (vonder Embse et al., 2021), concluding that exposure to DDT and DDE produces a decrease in the thermogenesis of brown adipose tissue in rodents. However, in other studies such as Al-Obaidi et al. (2022), performed in rats, a reduction in the browning of white adipose tissue has been observed, with no changes in thermogenesis in brown adipose tissue after 5 weeks of treatment with DDT or DDE.

Today it is known that the composition of the intestinal microbiota plays a key role in the development of obesity. In this context, ingested organochlorines can modify the composition thereof, generating dysbiosis (Popli et al., 2022). Thus, it has been observed that chronic exposure of adult

mice to a low dose of DDE for 8 weeks influences the relative composition and diversity of the intestinal microbiota, and alters bile acid metabolism (Liu et al., 2017). Specifically, elevated levels of *Firmicutes*, especially *Lactobacillus*, were found. There was also an increase in *Proteobacteria* and a decrease in *Bacteroidetes*, *Verrucomicrobia*, *Actinobacteria* and *Candidatus saccharibacteria*. At the genus level, the relative abundance of *Parabacteroides, Prevotella, Bacteroides, Clostridium XIVa* and *Clostridium IV* decreased; while *Barnesiella, Alloprevotella, Oscillibacter, Lactobacillus, Parasutterella* and *Akkermansia* were increased (Liu et al., 2017). Changes in the composition of the microbiota result, in turn, in changes in the production of short-chain fatty acids, which may play a key role in the development of metabolic-based pathologies such as obesity and diabetes.

Human studies show that maternal organochlorine load can also influence the development of the intestine microbiota in infants through breast milk. Some studies have correlated high levels of DDT in the breast milk of Norwegian mothers with the abundance of the genus *Streptococcus* in infants, leading to a high likelihood of developing obesity (Iszatt et al., 2019). In addition, the high maternal burden of organochlorines has been shown to modify the colostrum microbiota in breastfeeding mothers, which eventually affects the microbial colonisation of the baby's intestine (Tang et al., 2019).

Numerous epidemiological studies have focused on the effects of organochlorine exposure on foetal programming. Thus, Verhulst et al. (2009) described a positive association between perinatal exposure to DDT and the development of overweight in 3-year-old boys and girls, and Warner et al. (2017) observed a similar association in 12-year-old children. Another study showed that while perinatal exposure to DDT was associated with the development of overweight in boys, that of its metabolite DDE was associated with overweight in 6-year-old girls (Valvi et al., 2012). In short, consistent scientific evidence indicating that prenatal exposure to DDE is associated with accelerated weight gain in childhood, and an increased risk of childhood obesity, has been found in more than 12 prospective studies (Vrijheid et al., 2016). Only three studies have found zero or negative associations between DDE exposure and childhood growth and obesity (Vrijheid et al., 2016). Maternal exposure to DDT has also been linked to the development of overweight in daughters when they reach the adult stage (45-53 years) (La Merrill et al., 2020). Recently, a meta-analysis has been published indicating that perinatal exposures to DDE and hexachlorobenzene were associated with higher BMI in children (Stratakis et al., 2022).

The effects of exposure to organochlorines may extend beyond the next generation. Thus, a study conducted on DDT-exposed rats showed that the descendants of the F1 generation did not develop obesity, while both male and female descendants of the F3 generation had obesity (Skinner et al., 2013). Likewise, some human studies have associated grandmothers' exposure to DDT with the development of obesity in the adult stage, in the second generation (Cirillo et al., 2021). Since exposure to organochlorines can affect foetal programming and induce changes that are seen in subsequent generations, it should be thought that they are likely to act through epigenetic mechanisms. Specifically, it seems that they can induce changes in DNA methylation, in specific areas called 5'-C-phosphate-G-3 (CpG) islands (Skinner et al., 2013).

Regarding studies in adult humans, there is ample evidence of the relationship between exposure to organochlorines and the development of obesity. A prospective study on young adults revealed

that DDE was associated with higher body mass index, measured 18 years after exposure (Lee et al., 2011). In the meta-analysis published by Cano-Sancho et al. (2017) seven prospective epidemiological studies were identified in which positive associations were found between DDE exposure and adiposity.

At the Duke University Diet and Fitness Centre in the United Kingdom, a study was conducted aimed at investigating whether weight reduction produced changes in plasma concentrations of organochlorines, or whether other factors, such as body fat distribution and history of weight cycles, were associated with baseline levels of organochlorines, in ten overweight women in a structured weight reduction program. The researchers found a positive association between DDT plasma concentrations and waist/hip index values, which remained significant even after adjusting for age (Frugé et al., 2016).

Table 6 shows a summary of the obesogenic effects of organochlorine pesticides demonstrated in the studies analysed in this report.

Table 6. Main findings of *in vitro*, *in vivo* and epidemiological studies on the obesogenic effects of organochlorine pesticides

Study type		Obesogenic effect	Reference
In vitro	- Murine 3T3-L1 preadipocytes - Human mesenchymal Stem cells	-↑ Adipogenesis -↑ Lipid accumulation -↑ Proliferation	Moreno-Aliaga and Matsumura (2022) Strong et al. (2015)
In vivo	Rodents - C57Bl/6 mice (exposure of mothers in the gestational period) - Sprague-Dawley rats	In female offspring, in their adult stage: - ↓ Body temperature - ↓ Cold tolerance - ↓ Energy expenditure - ↓ Thermogenesis in brown adipose tissue - ↓ Browning of white adipose tissue - Changes in the intestinal microbiota	La Merrill et al. (2014; Vonder-Embse et al. (2021) Al-Obaidi et al. (2022) Liang et al. (2019)
Human	- Epidemiological - Intervention	-↑ Body weight (overweight/obesity) - Changes in baby's microbiota (for breastfeeding mothers)	Verhulst et al. (2009); Lee et al. (2011); Valvi et al. (2012); Lee (2012); Skinner et al. (2013); Vrijheid et al. (2016); Warner et al. (2017); Cano-Sancho et al. (2017); Iszatt et al. (2019); Tang et al. (2019); La Merrill et al. (2020); Stratakis et al. (2022); Cirillo et al. (2021)

7.4 Summary of scientific evidence and comments

Existing scientific evidence supports the obesogenic effect of organochlorine pesticides. Although there are many molecules included in this group, most of the studies have focused on DDT and its metabolite DDE. While it is true that its use is no longer allowed, it is possible that, due to its high

persistence in the environment, people who were exposed to these substances for a long time, or even people whose mothers or grandmothers were exposed to them, can now develop excess body weight. However, it must be considered that the study of organochlorines is extremely complex since the plasma concentrations of DDT and DDE are affected by factors that govern their excretion, as well as factors related to lipid turnover (cycles of loss and body weight gain). Indeed, in addition to age, which can serve as an index of cumulative exposure to these exceptionally stable compounds, factors associated with lipid mobilisation can modify the exposure of tissues that are specific targets of these compounds.

8. Flame retardants

8.1 Description and uses

Polybrominated diphenyl ethers (PBDEs) began to be commercialised in the 1960s and were produced commercially as mixtures of the three: penta-, octa- and deca-PBDEs (Kajiwara et al., 2008). There are 209 congeners (Pietron and Malagocki, 2017). They were widely used in numerous commercial and domestic polymer-based products, such as textiles, furniture and electronics, as fire retardants (Shaw and Kannan, 2009) (Chang et al., 2020). These compounds have been included in the list of persistent organic pollutants of the United Nations Stockholm Convention since 2009 (UNEP, 2009). Mixtures of octa- and penta-PBDEs were banned in 2004, while deca-PBDEs was phased out as of 2013 (Madgett et al., 2022). The main routes of exposure to these compounds are animal foods (mainly fish) and household dust (Pietron and Malagocki, 2017).

8.2 Food exposure

Although its mass production was conducted at the beginning of the 21st century, and its prohibition has been one of the last within persistent contaminants, it is interesting to note that the concentrations of PBDEs found in food are lower than, for example, the PCBs, that ceased their production more than 30 years ago. This was pointed out in a study by Ceci et al. (2022), in which, except for pork, even in the most contaminated fish and seafood samples, the concentration of PBDEs is an order of magnitude less than that of PCBs. These authors also found this lower PBDEs contamination compared to other persistent compounds such as PBDD/Fs. Similar results were found in other marine food studies (Fernandes et al., 2009).

In another recent study, PBDEs content in food over the last decade (2012-2022) has been reviewed (Marques et al., 2022). Although the comparison is complicated due to the great variability of the analytical methods used, there seems to be a general tendency to decrease the levels of PBDEs in food and, consequently, the dietary intake of these contaminants. However, a full risk assessment cannot be conducted due to the absence of TDI for these compounds. However, there are reference values for some congeners. Considering the effects of PBDEs on neurodevelopment as a critical endpoint, EFSA identifies the Benchmark Dose (BMD) and its corresponding 95 % lower confidence limit for a 10 % baseline response, Benchmark Dose Lower Bound (BMDL10s), for the following PBDE congeners: PBDE-47, 309 µg/kg b.w., PBDE-99, 12 µg/kg b.w., PBDE-153, 83 µg/kg b.w. and PBDE-209, 1700 µg/kg b.w. (EFSA, 2011). On the other hand, the EPA, in the U.S., has established

oral RfD for some PBDEs: 7, 3 and 2 µg/kg b.w./day for deca-PBDEs octa-PBDEs and penta-PBDEs, respectively (EPA, 2017).

8.3 Scientific evidence

Most PBDEs have antiandrogenic activity *in vitro* and in *vivo* (Stoker et al., 2005); tetra- and hexa-PBDEs have potent oestrogenic activity *in vitro*; hepta-PBDEs and 6-Hydroxy-2,2 ',4,4' -tetrabromodiphenyl ether (6-OH-BDE-47), a metabolite of PBDE-47, have antiestrogenic activity (Hamers et al., 2006). The obesogenic effects of PBDEs have been demonstrated in *in vitro* studies (Wen et al., 2019). Recently, PBDE-99 has been shown to stimulate the first phase of adipogenesis in C3H10T1/2 pluripotent stem cells (Wen et al., 2022). In rats, daily exposure to PBDE-71 has been observed to induce markers of insulin resistance, including increased lipolysis and reduced glucose oxidation in adipocytes (Hoppe and Carey, 2007). Maternal rodent exposure to PBDE-47 predisposed pups to increased body weight during early postnatal development and to the risk of metabolic dysfunction (Suvorov et al., 2009) (Wang et al., 2018b). It also triggered significant transcriptomic changes in gonadal adipose tissue, placing adipose tissue as a primary target of PBDE-47 (Abrha and Suvorov, 2018).

This obesogenic effect has also been observed in epidemiological studies, in which the accumulation of PBDEs in human adipose tissue is related to the development of obesity (Helaleh et al., 2018) (Valvi et al., 2020). Positive associations of several PBDEs congeners with adiposity measures were seen in boys exposed to PBDEs through the mother, in the case of boys with PBDE-153 only and in girls with PBDE-100 and PBDE-153. Breastfeeding duration was a determining factor, and it was observed that prenatal exposure to low levels of PBDEs can influence adiposity measures in childhood and that potential effects of PBDEs were attenuated by a breastfeeding period longer than 6 months (Chen et al., 2022).

Table 7 shows a summary of the obesogenic effects of flame retardants demonstrated in the studies analysed in this report.

Table 7. Main findings of *in vitro*, *in vivo* and epidemiological studies on the obesogenic effects of flame retardants

Study type		Obesogenic effect	Reference
In vitro	- H4IIE (rat hepatoma) - U-2 OS (human osteoblast) - T47D (human breast cancer) - 3T3-L1 (preadipocytes) - C3H10T1/2 mesenchymal stem cells	- Adipogenesis stimulation - ↑ PRARγ2 expression	Hamers et al. (2006); Wen et al. (2019); Wen et al. (2022)

Table 7. Main findings of *in vitro*, *in vivo* and epidemiological studies on the obesogenic effects of flame retardants

Study type		Obesogenic effect	Reference
In vivo	Rodents - Wistar rats - Sprague-Dawley rats - ICR mice - C57BL/6 (CD-1) mice	- ↑ Lipolysis - ↓ Glucose oxidation - ↑ Body weight - Metabolic dysfunction	Stoker et al. (2005); Hoppe and Carey (2007); Suvorov et al. (2009); Wang et al. (2018b); Abrha and Suvorov (2018)
Epidemiological	Human	- ↑ Adipose tissue	Helaleh et al. (2018); Valvi et al. (2020); Chen et al. (2022)

8.4 Summary of scientific evidence and comments

Although there is a trend of decreasing levels of all these persistent compounds, their presence in food remains of concern, due to the demonstrated obesogenic effects both in *vitro* and in *vivo* studies. For this reason, it is important that its prohibition is maintained and that controls are continued to ensure that the tolerable levels of these pollutants are not exceeded. Given the paucity of epidemiological studies observed, more work is needed to analyse the effect of human exposure to these compounds on metabolic diseases such as obesity.

9. Perfluorinated compounds (PFAs)

9.1 Description and uses

Perfluorinated compounds (PFAs) are artificial chemicals that have been used in industry and consumer products since the 1940s. More than 200 categories and subcategories of use have been identified for more than 1400 individual PFAs compounds, and some studies claim that there are more than 4000 of these compounds. PFAs are used in a variety of products, including non-stick cookware, water-repellent clothing, stain-resistant fabrics and carpets, some cosmetics, fire-fighting foams, and water, oil, and grease-resistant products. They are also used in lesser-known products such as ammunition, climbing ropes, guitar strings, artificial turf, and soil remediation (Sunderland et al., 2019) (Glüge et al., 2020).

The most studied PFAs compounds are perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS) and perfluorononanoic acid (PFNA), the latter two least studied (Glüge et al., 2020).

In 2010, perfluorooctane sulfonates (PFOS) were included in the Stockholm Convention, which aims to control persistent organic pollutants to protect human health and the environment, so their use should be restricted as much as possible. In 2020, Regulation (EU) No. 2020/784 was published amending existing EU legislation and restricting the use of persistent organic pollutants. The new regulation specifically limits the use of PFOA, its salts and related compounds. This regulation sets a maximum concentration of 0.025 mg/kg for PFOA and any salt thereof, and a maximum concentration of 1 mg/kg for PFOA-related compounds or a combination of those compounds (EU, 2020).

This was also taken into account when issuing Commission Recommendation (EU) 2019/794, which recommends the investigation of the presence of PFAs in food contact material, specifically its presence in paper and cardboard-based materials, such as those used to wrap fast food and bakery products and takeaways, and also popcorn bags (EU, 2019) (Ramírez-Carnero et al., 2021).

9.2 Food exposure

Perfluorinated substances are of concern because of their high persistence (or that of their degradation products) and their impact on human and environmental health which are known or can be inferred from some well-studied PFAs. People can be exposed to these halogenated compounds in different ways, including diet, being these substances most often found in drinking water, fish, fruit, eggs, and egg products. Children under 12 months of age are the most exposed population group, according to the EFSA scientific assessment of the risks to human health related to the presence of perfluorinated substances in food (2020). In addition, exposure during pregnancy and lactation is the main factor that may contribute to increased PFAs levels after birth.

In its 2020 report, the EFSA CONTAM Panel determined a TWI of 4.4 ng/kg b.w. applicable to the sum of the four PFAs with the longest half-life in the body (PFOA, PFOS, PFHXS, PFNA). This report shows that the mean exposure (lower confidence limit, LB) in different age ranges of adolescents and adults ranges from 3 to 22 ng/kg b.w./week, with a P95 of 9 to 70 ng/kg b.w./week, respectively. It is noteworthy that children showed twice as much exposure. Upper limit exposure (UB) was 4 to 49 times higher than LB levels; the latter being considered more reliable. Fish, fruits and products that incorporate them, and eggs and their products are the foods that contribute the most to exposure (EFSA, 2020).

9.3 Scientific evidence

PFAs can affect our biological system due to their structural similarity to fatty acids, the building blocks of fat in our body, as well as the foods we eat. They also act as endocrine-disrupting chemicals due to their ability to interfere with hormonal systems. Therefore, a first action could be linked to the alteration of lipid metabolism (Heindel and Blumberg, 2019) (Chen et al., 2020) (Aaseth et al., 2022).

Specifically, the laboratory data demonstrate that PFAs are potent inducers of adipogenesis through interference with PPARγ-activated gamma receptor signalling and other pathways, being more prominent in the case of sulfonated perfluoroalkyl acids, while the carboxylated agents showed fewer alterations in the gene expression of mouse 3T3-L1 cells (Watkins et al., 2015). A similar mechanism was responsible for the inhibition of osteogenic differentiation and stimulation of PFOA-induced hMSC adipogenesis (Liu et al, 2019b). In addition to PPARγ binding and associated increased adipogenesis (Yamamoto et al., 2015), PFOA was shown to increase PPARγ transcription and demethylation of PPARγ promoters during 3T3-L1 preadipocyte differentiation (Ma et al., 2018). A study on the nematode *Caenorhabditis elegans* also demonstrated an involvement of PPAR, mitogen-activated protein kinase (MAPK) and transforming growth factor beta (TGFβ) signalling

in the obesogenic effect of PFOA (Li et al., 2020). At the same time, an *in vivo* study of perinatal PFOA exposure demonstrated a sex-specific response with deeper metabolic alterations in female C57BL/6JxFVB mice (Van-Esterik et al., 2016). The observed adipogenic effects were accompanied by an increase in insulin-stimulated glucose uptake through the up-regulation of GLUT4 transporter and insulin receptor substrate 1 (IRS1) expression in murine 3T3-L1 preadipocytes (Xu et al., 2016). However, this observation contrasts with the results of an *in vivo* study demonstrating PFOA-induced insulin resistance in exposed Balb/c mice. It has been proposed that these effects may be mediated by the downregulation of protein kinase B (Akt) mRNA expression and its phosphorylation, as well as by increased mRNA expression and protein levels of phosphatase and homologous tensin (Du et al., 2018).

Similarly, PFOA and PFOS were shown to decrease the expression of osteopontin, osteonectin, osteocalcin, and β-catenin in human bone marrow-derived mesenchymal stem cells (hBMSCs), which is indicative of reduced osteogenesis, while expression of adipogenesis-specific marker genes PPARγ, C/EBPα, LPL, and leptin were up-regulated (Liu et al., 2019b). It was also seen that, in parallel to the induction of PPARγ and C/EBPα expression, PFOS-induced adipogenesis was associated with activation of the erythroid factor 2-related nuclear factor pathway (Nrf2) in murine 3T3-L1 preadipocytes (Xu et al., 2016). In addition to PPARγ, the proadipogenic effects of PFOS may involve the induction of the AB2 protein (Gao et al., 2020). On the other hand, PPARα and PPARβ mRNA expression can affect stem cell differentiation in hBMSCs (Zheng et al., 2021). Modulation of DNA methylation can also be considered a potential mechanism of the impact of PFOS on adipogenesis (Van den Dungen et al., 2017).

A potential adipogenic effect has been demonstrated for other PFAs. Specifically, perfluorobutanesulfonic acid (PFBS) used as a substitute for PFOA can be a proadipogenic agent, promoting the differentiation of 3T3-L1 preadipocytes to adipocytes, by upregulating the transcription factors PPARγ and C/EBPα and the acetyl-CoA carboxylase and the lipogenic fatty acid synthase (Qi et al., 2018). Compared to PFOS, chlorinated polyfluorinated ether sulfonates (Cl-PFAES) manifested great adipogenesis-stimulating potential in 3T3-L1 through the PPARγ pathway (Li et al., 2018). Perfluorinated alkyl acids (PFAAs) also showed the ability to induce adipogenesis in 3T3-L1 cells at human blood exposure levels (Xie et al., 2023).

Other studies in rodents and zebrafish confirm the obesogenic effect of PFAs (Kudo and Kawashima, 1997) (Du et al., 2009) (Marques et al., 2020) (Sant et al., 2021). It has been shown in rodent studies that PFAs participate in the regulation of PPAR genes related to the metabolism of fatty acids, glucose and glycogen in peroxisomes, and in the biosynthesis of cholesterol and bile acids (Rosen et al., 2008, 2009). In addition, in mice, prenatal exposure to PFAs increases serum leptin and insulin levels and weight in middle adulthood (Hines et al., 2009).

PFOA exposure could be associated with six disease categories: hypercholesterolemia, thyroid disease, ulcerative colitis, testicular cancer, kidney cancer, and pregnancy-induced hypertension (Steenland et al., 2020). Likewise, prenatal exposure to PFAs compounds could be linked to obesity, metabolic disorders, and growth disturbances in the infant population (Halldorsson et al., 2012) (Braun, 2017) (Lauritzen et al., 2018). Recent studies on the associations between gestational PFAs

concentrations and childhood adiposity in a diverse cohort of mothers and children show that certain PFAs [PFOS (5.3 ng/ml), PFOA (2.0 ng/ml) and fluoroundecanoic acid (PFUnDA)] can be defined as potential obesogenic compounds in the infant population due to the ability to cross the placenta and affect the fetus with postnatal effects on adiposity, said condition being modified according to maternal race and/or ethnicity (Bloom et al., 2022).

A recent literature review (Qi et al., 2021) identified 22 studies linking exposure to these compounds to obesity. Approximately 2/3 of the studies showed positive associations between exposure to perfluoroalkylated and polyfluorinated substances, and the prevalence of obesity and/or type II diabetes mellitus. In a multicenter prospective cohort study, the European Youth Heart Study, conducted on young participants (n= 369), scientists stated that exposure to PFOS and PFOA predicted adiposity at 15 and 21 years (Domazet et al., 2016). A recently published cross-sectional study on U.S. children aged 12 to 18 years (n= 2473) showed a dose-dependent association between obesity and PFAs exposure (Geiger et al., 2021). However, EFSA reported in the 2020 publication that insufficient data were available to support a relationship between PFAs exposure and obesity, so the claim to this association (PFAs *versus* Obesity) requires more research and a greater number of epidemiological studies to give greater scientific evidence (EFSA, 2020) (Aaseth et al., 2022).

Table 8 shows a summary of the obesogenic effects of PFAs demonstrated in the studies analysed in this report.

Table 8. Main findings of *in vitro*, *in vivo* and epidemiological studies on the obesogenic effects of PFAs

Study type		Obesogenic effect	Reference
In vitro	- 3T3-L1 cells - Human bone marrow mesenchymal stem cells (hBMSCs)	- ↑ Adipogenesis - Inhibition of osteogenic differentiation - ↑ PPARγ transcription - ↑ Demethylation of PPARγ promoters - ↓ Expression of osteopontin, osteonectin, osteocalcin and β-catenin - ↓ Osteogenesis - ↑ Ap2 protein	Watkins et al. (2015); Liu et al. (2019b); Yamamoto et al. (2015); Ma et al. (2018); Xu et al. (2016); Gao et al. (2020); Zheng et al. (2021); Van den Dungen et al. (2017); Qi et al. (2018); Li et al. (2018); Xie et al. (2023)
In vivo	Rodents - Balb/c mice - C57BL/6J mice - Std:ddY mice - CD-1 Mice - Rats without PPARα Nematode (*Caenorhabditis elegans*)	- ↑ Adipogenesis - ↑ Leptin and insulin - ↑ Weight - ↑ Glucose uptake - Insulin resistance - ↓ mRNA expression of protein kinase B (Akt) and its phosphorylation - ↑ mRNA expression - ↑ Phosphatase protein and homologous tensin	Li et al. (2020); Van-Esterik et al. (2016); Du et al. (2018); Kudo and Kawashima (1997); Marques et al. (2020); Hines et al. (2009); Rosen et al. (2008, 2009)

Table 8. Main findings of *in vitro*, *in vivo* and epidemiological studies on the obesogenic effects of PFAs

Study type		Obesogenic effect	Reference
Epidemiological	Human	- Hypercholesterolemia - Thyroid disease - Ulcerative colitis - Testicular cancer - Kidney cancer - Pregnancy-induced hypertension - Obesity - Growth disorders - Metabolic alterations - ↑ Adiposity - Diabetes mellitus type II	Steenland et al. (2020); Halldorsson et al. (2012); Braun et al. (2017); Lauritzen et al. (2018); Bloom et al. (2022); Qui et al. (2020); Domazet et al. (2016); Geiger et al. (2021); Aaseth et al. (2022)

9.4 Summary of scientific evidence and comments

Overall, existing *in vitro* and *in vivo* data demonstrate that exposure to PFOS and/or PFOA may promote adipogenesis through up-regulation of PPARγ and C/EBPα signalling, thus contributing to an increased risk of obesity, although epidemiological data appear to support this effect.

10. Metals

10.1 Description and uses

Metals can appear as contaminants in food from their presence as components of the earth's crust, from natural phenomena such as volcanic eruptions, as a result of human activities such as agriculture, or from contamination during food processing and storage (EFSA, 2023).

10.2 Food exposure

Non-occupational population exposure to heavy metals occurs through different routes, being food and contaminated water the main sources (Yilmaz et al., 2020).

The levels of metals consumed through diet depend on various factors such as the mineral composition of the soil where the food is grown, climatic conditions, the composition of the water for irrigation and agricultural practices (e.g. types and amounts of fertilisers used, as in the case of cadmium (Cd)). Processing and packaging may also have an influence in certain cases such as aluminium (Al) and tin (Sn) of canned foods (Freire et al., 2020). The most common metal-containing foods in the diet are fish and seafood, vegetables and grains, chocolate and coffee, fruits, mushrooms and mushrooms (Dedoussis, 2015).

10.3 Scientific evidence

Human exposure to certain metals such as arsenic (As), cadmium (Cd) and lead (Pb) has been associated with metabolic alterations: increased risk of type II diabetes mellitus, cardiovascular disease and obesity (González-Casanova et al., 2020). It appears that adipose tissue is the potential target for obesogenic contaminants, including toxic metals, so various obesity-related metabolic

alterations could be associated with the presence of these metals in this tissue (Tinkov et al., 2015). *In vivo* and *in vitro* studies have shown that heavy metals can affect adipose tissue mass and function by modulating adipogenesis through PPARγ and C/EBP expression (Egusquiza and Blumberg, 2020). If exposure occurs at low levels, individuals can up-regulate key adipogenic factors, such as PPARγ, thus promoting excessive adipogenesis and contributing to obesity. It has been observed that, with higher metal exposures, adipogenesis can be inhibited through down-regulation of C/EBP and PPARγ (Tinkov et al., 2021). Thus, the effects of heavy metals on adipogenesis may be dose-dependent. Thus, it has been observed that when the exposure is conducted at low doses there is an increase in adipogenesis (Park et al., 2017) (Lee, 2018), while at higher doses there is an inhibition of the differentiation of adipose tissue, an effect qualified as "anti-obesogenic" (Rizzetti et al., 2019). This anti-obesogenic effect has been demonstrated especially for mercury (Hg) by reducing adipocyte size (Rizzetti et al., 2019), adipokine secretion and activation of apoptosis through induction of oxidative stress (Chauhan et al., 2019) and regulation of genes related to adipogenesis.

The effects of As, especially As (III) in its inorganic forms, on the various metabolic and physiological processes that take place in white adipose tissue and that are altered in obesity, such as adipocyte growth, adipokine secretion, lipid metabolism and glucose metabolism, are known. Hence, since As can negatively affect the metabolism of white adipose tissue, it can be pointed out that this metalloid is a potential obesogen (Ceja-Galicia et al., 2017). Various *in vitro* or mechanistic studies suggest several pathways by which As might exert these adverse effects, depending on concentration, on pancreatic β-cell function and insulin sensitivity, oxidative stress and effects on glucose uptake and transport, gluconeogenesis, adipocyte differentiation, and calcium (Ca^{2+}) signalling (Thayer et al., 2012). Hou et al. (2013) exposed 3T3 L1 cells to this metal and found that it can inhibit adipogenesis by activating CHOP10, a molecule that inhibits the transcriptional activity of C/EBPβ, thus causing the suppression of adipogenesis. CHOP10 is a protein that increases its expression in response to endoplasmic reticulum stress caused by protein misfolding. Similarly, Beezhold et al. (2017) demonstrated that As can increase the expression of the MicroARN, microRNA 29b-1 (miR-29b), involved in the regulation of the cell cycle and in the increase of cyclin D1 expression, resulting in the inhibition of differentiation towards the fat cell (González-Casanova et al., 2020). Its mechanism of action could be the promotion of weight gain by hypertrophy of adipocytes directly or primarily.

Pb has been considered obesogenic for its adipotropic effects on adipose tissue (Tinkov et al., 2021). *In vivo* and *in vitro* studies have shown that Pb accumulates in human adipose tissue causing a significant increase in bone marrow adiposity characterised by increased adipocyte size and number through up-regulation of PPARγ gene expression (Betanzos-Robledo, 2022). On the other hand, in rats exposed to low concentrations of Pb before conception and for 18 months, it was observed that this heavy metal could stimulate differentiation in mesenchymal cells to mature adipocytes with a concomitant detriment of osteoblastogenesis. This process was further characterised by an inhibition of the Wnt/β-catenin cell signalling pathway. More recently, the proadipogenic effect of Pb was demonstrated in 3T3-L1 cultures, which involved activation of the C/EBPβ and PPARγ pathways (Martini et al., 2018).

Among the different forms of Hg, alkyl Hg is more soluble in lipids and crosses biological membranes, with methylmercury (MeHg) being the dominant form in human blood (Jung et al., 2013) since the primary source of exposure for the general population is fish consumption. At low doses, Hg exposure modifies adipokine secretion, increases levels of resistin, adiponectin, and the lipid peroxidation product 4-hydroxynonenal (4-HNE), decreases the number of adipocytes and lipid droplets pooled together, and results in activation of apoptosis through induction of oxidative stress and systemic inflammation (Chauhan et al., 2019). In addition, exposure to mercury causes alterations in carbohydrate and lipid metabolism. These effects could lead to an increased risk of developing obesity-related metabolic alterations (Shin et al., 2018). Exposure to MeHg inhibits paraoxonase-1, which prevents the atherosclerotic process by metabolising toxic oxidised lipids associated with LDL and HDL (Ayotte et al., 2011). Thus, Hg induces oxidative stress and disrupts gluconeogenesis, resulting in systemic inflammation that promotes the accumulation of abnormal adipocytes (Maqbool et al., 2016).

Although Cd is primarily considered nephrotoxic, there are a large number of short- and long-term *in vivo* Cd exposure models demonstrating significant correlations between Cd exposure and the prevalence of prediabetes and/or type 2 diabetes mellitus (Schwartz et al., 2003). While the exact mechanism of action of Cd-induced alteration of glucose homoeostasis is unknown, it is likely related to general pancreatic β cell dysfunction and impaired glucose-stimulated insulin release in animal models (Nguyen et al., 2022).

There are several epidemiological studies linking metal exposure to obesity and its complications. Based on epidemiological studies from the mid-1990s, As has been associated with an increased risk of developing type 2 diabetes mellitus in humans, especially in those areas where exposure levels were highest (Kile and Christiani, 2008) (Wang et al., 2014). In particular, a prospective study conducted in Taiwan on people exposed and not exposed to As through drinking water showed that the relative multivariate risk of diabetes was 2.3 (1.2-4.3) for a BMI≥ 25 *versus* <25 kg/m^2 (Tseng et al., 2000). Although these studies have not specifically evaluated the obesogenic effect, obesity is one of the main risk factors for the development of type 2 diabetes.

Transgenerational effects of As include alterations in birth weight, increased postnatal weight gain with elevated body fat content, glucose intolerance, insulin resistance, and increased serum triglycerides. Elevated leptin has been observed in umbilical cord blood, placenta, and postnatal serum levels (Heindel et al., 2017). There is also evidence that As may interact with other environmental factors, such as high-fat diets (Paul et al., 2011) or folate-related nutrients (Heck et al., 2007) to positively or negatively modulate its obesogenic effects or other diseases related to this metalloid. In addition, the metabolism of As also plays a key role in its biological effects, being influenced both by polymorphisms in the enzymes involved, particularly methyltransferase (known as AS3MT) (Douillet et al., 2013), and by BMI, although there is controversy on the latter point. Therefore, based on all the findings presented, arsenic is a potential obesogen, although more studies are needed to address this problem accurately (Ceja-Galicia et al., 2017). In another order of things, Kuo et al. (2015) suggest that conversion to an atherogenic lipid profile in adolescents may be associated with early exposure to environmental As, particularly during the preadolescent period and recommend an early environmental modification approach to prevent As-related cardiovascular disease. Howe-

ver, whether atherogenic lipids related to As exposure continues into adulthood is unknown.

Cd, Pb and As exposures are associated with smaller size at birth (Erkin-Cakmak et al., 2015), which constitutes a risk factor for subsequent weight gain and increased adiposity. Prenatal exposure to toxic metals is also linked to higher levels of leptin at birth (Gossai et al., 2015). Moreover, there is evidence that early life stages such as foetal life, childhood, childhood, and adolescence are critical periods in which environmental exposures may have a long-term phenotypic effect (Rauschert et al., 2017).

Huang et al. (2022) investigated the association between joint in uterus exposure to Hg, Pb, Cd, and overweight or obese children, and the possible protection of adequate maternal micronutrients (selenium and folate) in 1442 low-income, Black, and Hispanic urban U.S. mother-child pairs, and prospective follow-up through age 15. The results showed that, in this cohort of American children at elevated risk of exposure to toxic metals and obesity, there were individual positive associations of maternal Hg and Pb exposure with offspring obesity, as well as a positive dose-response association between in uterus co-exposure to all three toxic metals and childhood obesity. In particular, the metal-blend-obesity association was more pronounced in children born to mothers with obesity. However, adequate maternal selenium and folate levels mitigated the risk of childhood obesity.

Betanzos-Robledo et al. (2022) assessed the possible modification of fat accumulation in adolescence after exposure to Pb and Hg and concluded that such exposure may alter adiposity in later life. In adolescents with obesity, exposure to Pb increases the accumulation of subcutaneous and visceral fat, effects that were not observed in individuals with a normal BMI. These results coincide with other previous epidemiological studies. Thus, a cross-sectional study on 5558 adults showed a positive association between blood Pb levels with BMI and obesity in women (Wang et al., 2015). However, in another cohort study on 299 children evaluated from birth, blood Pb levels were associated with a lower BMI at the ages of 2 to 3 years (Cassidy-Bushrow et al., 2016).

Exposure to Hg affects abdominal and subcutaneous fat in obese adolescents. A cross-sectional study on elderly Koreans living in coastal areas revealed a positive association between blood mercury and waist-to-hip ratio (You et al., 2011). However, in the Korean National Health and Nutrition Examination Survey (KNHANES) study, blood Hg was positively associated with visceral adiposity but negatively associated with body fat percentage (Park and Lee, 2012). According to WHO data, background Hg levels in the general population are <5 µg/l (Basu et al., 2018). Currently, the health impact of Hg exposure focuses more on chronic, low or moderate level exposure than on the hazard and effects of low-grade Hg exposure (Ye et al., 2016). Studies in this regard showed that, in overweight adolescents, as Hg exposure increased, all types of fat deposits decreased, although the differences were not statistically significant. This pattern does not imply that Hg protects against fat accumulation among overweight adolescents or has an anti-obesogenic character.

Lee (2018) showed that mercury exposure is significantly associated with hyperlipidaemia and increased liver enzymes; blood Hg levels were significantly higher ($p < 0.0001$) in the hyperlipidaemia group (male: 4.03 µg/l, female: 2.83 µg/l) than in the group without hyperlipidaemia (male: 3.48 µg/l, female: 2.69 µg/l). A 1 µg/l increase in blood Hg was associated with an 11 % increase in the odds of hyperlipidaemia, even after adjustment for drug treatment.

The relationship between Cd exposure and obesity is not well studied and appears to be more complex. A negative correlation between blood Cd levels and BMI was observed in Chinese people (Nie et al., 2016). However, other works have shown that exposure to Cd at levels reflecting human exposure over a lifetime, results in diabetogenic and obesogenic effects. Determining how Cd alters body weight and, specifically, white adipose tissue weeks after the last dose of Cd is of great interest (Nguyen et al., 2022). Green et al. (2018) determined Cd levels in maternal blood samples from the first trimester and analysed the results cross-over with the weight gain trajectory of children up to 5 years. The role of Cd as a potential obesogen in an *in vivo* zebrafish model was then analysed. The results showed that the presence of Cd in maternal blood during pregnancy could be associated with an increased risk of juvenile obesity in offspring, regardless of other variables, including Pb and smoking. These results are consistent with a parallel study on a zebrafish model where a positive association of this metal with adiposity accumulation was found (Beier et al., 2013), demonstrating that Cd may be an obesogen in humans, and that prenatal human exposure to Cd likely initiates a cascade of molecular events leading to increased adiposity.

Epidemiological and animal studies over the past 15 years have shown that in uterus and neonatal Cd exposures alter the programming of endocrine systems involved in growth, energy metabolism, adipogenesis, appetite, and glucose-insulin homoeostasis of the developing foetus (Tomar et al., 2015) (Lin et al., 2017). Cd exposure has been associated with lower birth weight (Vidal et al., 2015) (Everson et al., 2016), a phenomenon known to be a persistent risk factor for an accelerated increase in adiposity in young children, which has been linked to cardiometabolic impairment in adulthood (De Kroon et al., 2010).

Table 9 shows a summary of the obesogenic effects of the metals demonstrated in the studies analysed in this report.

Table 9. Main findings of *in vitro*, *in vivo* and epidemiological studies on the obesogenic effects of metals

Study type		Obesogenic effect	Reference
In vitro	As 3T3 L1 cells	* Adverse effects on: - Pancreatic β-cell function - Insulin sensitivity - Oxidative stress - Glucose uptake and transport - Gluconeogenesis - Adipocyte differentiation - Calcium signalling * Inhibits adipogenesis by CHOP10 activation * ↑ 29b-1 microRNA expression	Thayer et al. (2012); Hou et al. (2013); Beezhold et al. (2017)
	Pb 3T3-L1 cultures	- Proadipogenic effect: activation of C/EBPβ and PPARγ pathways	Martini et al. (2018)
	Hg Adipocytes 3T3-L1 Islets of Langerhans	- ↑ Resistin, adiponectin and 4-hydroxynonenal levels - ↓ No. of adipocytes and pooled lipid droplets - Activation of apoptosis by induction of oxidative stress and systemic inflammation - Interruption of gluconeogenesis: accumulation of abnormal adipocytes	Chauhan et al. (2019); Maqbool et al. (2016)
In vivo	Pb Rat	-↑ Differentiation in mesenchymal cells to mature adipocytes -↓ Osteoblastogenesis	Martini et al. (2018)
	Hg Wistar Rats	- High doses inhibit the differentiation of adipose tissue: "anti-obesogenic"	Rizzetti et al. (2019)
	Cd Db/Db Mice and Rats Zebrafish	- Pancreatic β-cell dysfunction - Impaired glucose-stimulated insulin release - Positive association with adiposity accumulation	Nguyen et al. (2022); Beier et al. (2013)

Table 9. Main findings of *in vitro*, *in vivo* and epidemiological studies on the obesogenic effects of metals

Study type		Obesogenic effect	Reference
Epidemiological	As Humans	-↑ Weight by adipocyte hypertrophy - Increased risk of developing diabetes mellitus 2 in areas with ↑ exposure levels (water) - Changes in birth weight, ↑ postnatal body with ↑ fat weight, glucose intolerance, insulin resistance, ↑ serum triglycerides, ↑ leptin levels	González-Casanova et al. (2020); Wang et al. (2014); Heindel et al. (2017)
	Pb Humans	- ↑ Bone marrow adiposity: increased size and number of adipocytes → positive regulation of PPARγ expression - Lower birth weight - ↑ Leptin levels - Positive association of maternal exposure and offspring obesity - ↑ Subcutaneous and visceral fat accumulation in obese adolescents - Positive association between blood levels of Pb and BMI and obesity in women	Betanzos-Robledo et al. (2022); Erkin-Cakmak et al. (2015); Huang et al. (2022); Wang et al. (2015)
	Hg Humans	- Alterations in carbohydrate and lipid metabolism - MeHg inhibits paraoxonase-1 - Positive association of maternal exposure and offspring obesity - Low-dose: ↑ adipogenesis - At high doses: inhibits the differentiation of adipose tissue	Shin et al. (2018); Ayotte et al. (2011); Huang et al. (2022); Rizzetti et al. (2019)
	Cd Humans	- ↑ Prevalence of prediabetes and/or diabetes mellitus 2 - Lower birth weight - ↑ Leptin levels - Alteration of endocrine growth systems, energy metabolism, adipogenesis, appetite and homoeostasis of developing foetal glucose-insulin	Schwartz et al. (2003); Gossai et al. (2015); Lin et al. (2017)

10.4 Summary of scientific evidence and comments

The obesogenic potential of heavy metals seems to be related to their accumulation and effects on adipose tissue, producing metabolic alterations related to obesity. Heavy metals can affect the

mass and function of adipose tissue by modulating adipogenesis. However, these effects may be dose-dependent.

The obesogenic mechanism of action of As could be the promotion of weight gain by hypertrophy of adipocytes directly or primarily. In turn, Pb accumulates in human adipose tissue causing a significant increase in bone marrow adiposity characterised by increased size and number of adipocytes, while Hg induces oxidative stress and disrupts gluconeogenesis, resulting in systemic inflammation that affects the accumulation of abnormal adipocytes. Finally, significant correlations between Cd exposure and the prevalence of prediabetes and/or type 2 diabetes mellitus have been demonstrated.

Early life stages, such as foetal life, infancy, childhood, and adolescence, are critical periods in which environmental exposures can have a long-term phenotypic effect. Thus, the presence of Cd in maternal blood during pregnancy could be associated with an increased risk of juvenile obesity in offspring.

Exposures to Cd, Pb and As are associated with smaller size at birth which constitutes a risk factor for subsequent weight gain and increased adiposity.

The conflicting data provided in the different studies invite further work to elucidate the role of heavy metals as obesogens.

11. Triclosan

11.1 Description and uses

Triclosan (TCS) is a broad-spectrum synthetic antimicrobial agent, licensed in the 1960s and used in hospital settings since 1972. It is part of the formulation of household, personal care and industrial products such as toothpaste and dental rinses, liquid soaps, laundry detergents, kitchen cutting boards and plastics in furniture, toys and sporting goods (Ley et al., 2017) (González-Casonova et al., 2020). In addition, it is frequently found in food and aquatic environment (Bedoux et al., 2012) (Pérez et al., 2013).

11.2 Food exposure

The population can be exposed to TCS both by direct contact with personal hygiene products, as well as through food, drinking water and dust (Chen et al., 2019). Indeed, it has been frequently detected in common biological samples, such as urine, blood, nails and fatty tissue, milk and blood from lactating women (Pycke et al., 2014) (Li et al., 2015). Due to the ability of TCS to penetrate and remain in tissues (21-hour half-life), its concentration in these is high enough to induce harmful effects for humans (Weatherly and Gosse, 2017).

Its effectiveness as an antibacterial has been called into question in 2016 by the FDA (Food and Drug Administration), which established rules prohibiting the use of triclosan in antibacterial products for hands and body, citing a lack of evidence to support its effectiveness as an antiseptic. The European Union banned TCS in all biocidal products for human hygiene as of January 2017 (Juncker, 2016). However, it is widely used in toothpaste as this agent helps fight gingivitis (Al Habashneh et al., 2017). Moreover, TCS has been found to be capable of producing bacterial resistance, decrea-

sing its inhibitory effect (Drury et al., 2013) (Nietch et al., 2013), both for itself and for other antimicrobials, including antibiotics in clinical settings (Suller and Russell, 2000).

Women tend to exhibit higher concentrations of TCS than men, and the age group with the highest TCS concentrations is 20 years (Yin et al., 2016). The body loads of TCS differ greatly depending on the site where it is determined (skin, blood or urine), the concentration of exposure and the type of exposure. After the use of mouthwashes or toothpastes containing TCS, plasma levels of TCS increase rapidly (Sandborgh-Englund et al., 2006).

A potential source of environmental exposure to TCS is the application of biosolids in agriculture. Due to the disposal of products containing TCS by drains, it accumulates in the sludge derived from treatment in wastewater treatment plants (WWTPs). Another part is transformed into products such as mTCS (triclosan-methyl) (Heidler and Halden, 2007). Triclosan-methyl is more lipophilic than TCS and exhibits greater potential for bioaccumulation in aquatic organisms (Rüdel et al., 2013) (Macherius et al., 2014). Triclosan-methyl has been detected in river fish samples in Germany (Rüdel et al., 2013) with mean levels in fish muscle tissue ranging from 70.8 to 378 ng/g (lipid weight). Wu et al. (2013) demonstrated that TCS accumulates in common vegetable roots (lettuce, spinach, cucumber and pepper). It should be considered that, due to the abiotic photodegradation of the dissociated form of TCS, there are multiple additional decomposition products of TCS, including dioxins (Fang et al., 2014).

11.3 Scientific evidence

Laboratory studies have suggested that TCS may influence energy metabolism by multiple mechanisms, being a potential obesogen, although the effect on obesity risk has not been well researched in humans (Han et al., 2021).

Regarding its influence on adipocyte differentiation, TCS has been shown to have an adipogenesis-inhibiting effect in a model with hMSCs, and this antiadipogenic effect was concentration-dependent, decreasing the production of markers typical of cellular fat, such as adiponectin and lipoprotein lipase (Guo et al., 2012).

In vivo and *in vitro* studies have suggested that TSC is likely to affect energy metabolism and subsequently adipogenesis as it may produce endocrine disruption (Huang et al., 2014) (Ley et al., 2017). Thus, in rats, triclosan reduces levels of both triiodothyronine (T3) and thyroxine (T4) (Ley et al., 2017). Decreased production of endogenous thyroid hormones has been associated with excess adiposity in adults (Kalloo et al., 2018). In addition, it has been observed that they present oestrogenic activity (Huang et al., 2014), which is linked to the development of obesity (Leeners et al., 2017).

As a biocide, TSC has the ability to alter the human microbiome. Ma et al. (2020) demonstrated that perinatal exposure to triclosan could cause a reduction in diversity and an alteration in the composition of the intestinal microbiota in adult rats. In a randomised intervention study, infants with higher TSC levels showed *Proteobacteria* species enrichment (Ribado et al., 2017). Disruption of the intestine microbiome and dysbiosis may be associated with an increased risk of childhood obesity (Parekh et al., 2015).

Several studies have been conducted to establish the relationship of triclosan with obesity, which have provided discrepant results. A study using NHANES data from 2007 to 2010 showed no asso-

ciation between triclosan and BMI *z-score*, hip waist circumference, and risk of obesity in 1298 children and adolescents (Buser et al., 2014). A cross-sectional study found no significant association between urinary concentrations of triclosan and adiposity risk among 76 Indian children (Xue et al., 2015). There were no significant differences in urinary concentrations of triclosan between the obese and normal groups among 151 Belgian adults (Geens et al., 2015). Three prospective cohort studies found no associations between urinary concentrations of triclosan during pregnancy and the risk of childhood overweight or obesity (Philippat et al., 2014) (Buckley et al., 2016) (Kalloo et al., 2018). However, two studies using NHANES data found conflicting associations between urinary triclosan and obesity among the general U.S. population (Lankester et al., 2013) (Li et al., 2015). One study found higher BMI values among subjects with the presence of urinary triclosan (Lankester et al., 2013), while another found lower BMI and WC values among subjects with detectable triclosan (Li et al., 2015). The discrepant results may be related to different sample sizes, population under study (children, adults, elderly, or pregnant women), study design (cross-sectional design *versus* prospective design), and urine type (morning urine *versus* punctual urine).

More recently, Han et al. (2021) determined the first-morning urine levels of 458 school-age children aged 7-11 who entered a dynamic cohort of children established in Shanghai in 2019 and 2020, using BMI and waist circumference to identify general overweight/obesity and central obesity, respectively. The results indicated that exposure to triclosan was associated with an increased risk of childhood obesity. Specifically, triclosan showed a trend of positive association with central obesity.

11.4 Summary of scientific evidence and comments

Exposure to TCS antimicrobial takes place through the personal hygiene products that contain it, as well as food and water. Its presence in wastewater favours its incorporation into food and the environment.

On its role as an obesogen, the studies conducted have led to contradictory results. Given the ubiquitous presence of TCS in the environment and its potential public health implications, further interdisciplinary studies are needed to document the health consequences of TCS exposure and identify the underlying mechanisms.

12. Microplastics

12.1 Description and uses

Traditionally, plastics have been considered inert due to their large molecular size, and concern about their potential harmful effects focused on their involvement as vectors of chemical pollutants, which can act as obesogens, as discussed in other sections of this report, as well as the ability to adsorb different pollutants and toxic compounds. However, the exposure of plastics to biological, chemical and physical conditions leads to their fragmentation into small pieces/particles, called microplastics (MPs, referring to plastic particles <5 mm) or nanoplastics (NPs, particles from 1 to 1000 nm) (EFSA, 2016b) (Hartmann et al., 2019). Given their origin, particles can be classified into primary micro(nano)plastics (MNPs), when intentionally manufactured (consumer products); or secondary MNPs, when released into the environment from the slow fragmentation/degradation of

larger plastics (Hartmann et al., 2019) (SAPEA, 2019). At present, the overlap of size ranges between NPs and MPs is still discussed, so the combined term MNPs is increasingly used in the scientific literature to refer to their potential impact on the human body and health. Fragmentation of plastic also facilitates the release of chemical molecules attached to its surface, such as chemical contaminants and associated additives. From a chemical point of view, these MNPs are complex mixtures containing multiple additives, such as plasticisers, flame retardants, stabilisers and pigments. Other chemicals may also be present in the MNPs, such as unreacted monomers, or unintentionally added substances. Finally, the MNPs may have adsorbed environmental contaminants and pathogenic microorganisms.

Most plastic particles are derived from petroleum, such as polypropylene (PP), polyethylene (PE), PVC, polyethylene terephthalate (PET) and polystyrene (PS). Currently, the dominant polymer types are fossil fuel-based plastics and less than 1 % are biodegradable; and of the nearly 370 million tonnes of plastic produced annually, only a small fraction (≈1 %) is bio-based (European Bioplastics, 2021).

12.2 Food exposure

Three main routes of exposure to MNPs have been proposed: inhalation, ingestion and dermal absorption. The reported concentrations of MNPs in various sources of human exposure (air, indoor dust, cosmetics, drinking water and other beverages, fish, molluscs or crustaceans, honey, salt, sugar and other dietary sources) according to the recent literature, suggest that food and beverages are one of the main sources of exposure to these contaminants. The recent report published by AESAN includes a comprehensive review of the presence of MPs in food and beverages, and dietary exposure to plastics that enter the food chain after polluting the environment (AESAN, 2019). Plastic particles that contaminate the food chain can have different origins, so several sources of contamination have been suggested: i) MNPs can be ingested directly by marine and terrestrial organisms, and also be absorbed by plants due to their small size, thus entering the food chain; ii) raw materials could be contaminated, such as water; iii) due to the presence of MNPs in the air, some of these particles could be deposited in food during processing, storage, transport or packaging (Wen et al., 2022). In fact, these contamination pathways are not mutually exclusive and could accumulate by conditioning the amounts of MNPs ingested through the diet.

12.3 Scientific evidence

One of the main difficulties in determining the risks of MNPs to human health is the lack of accurate information on exposure doses, mainly because that standardised methods for the quantitative determination of MNPs in air, water, food and cosmetics are still in development (Ramsperger et al., 2022). When inhaled or ingested, MNPs <20 µm in size can penetrate biological membranes, accumulate in tissues, and elicit cytotoxic and immune responses. Most of the available studies come from *in vitro* studies using cell models as well as animal models, but studies have also been published in human samples showing the biodistribution of MNPs through the blood (Leslie et al.,

2022), their accumulation in the liver, kidney, placenta and brain (Prüst et al., 2020) (Grodzicki et al., 2021) (Ragusa et al., 2021), as well as excretion through human faeces (Yan et al., 2022a).

Several recent studies have described the health risks of obesity-related exposure to MNPs in humans (recently reviewed by Kannan and Vimalkumar (2021), and Auguet et al. (2022)). To date, there are no *in vitro* studies on the effect of microplastics on obesity, although the substances that compose them such as those described in this report do exist. Among the various biological effects reported in laboratory animals from exposure to MNPs, adipogenesis and lipid metabolism through PPARγ activation suggests that exposure to MNPs could have an effect on obesity. Most of the studies come from murine models, and have focused especially on PS MNPs, followed by PE, while no studies are using other types of food-grade polymers, such as PET. In general, they indicate effects on adipocyte differentiation following accumulation in liver and kidney, and alterations in energy and lipid balance (Deng et al., 2017), or as demonstrated in *in vivo* studies in mice following exposure to PS MNPs, accompanied by some changes in the levels of key genes involved in lipogenesis and triglyceride synthesis in liver (Lu et al., 2018) (Auguet et al., 2022). Additives associated with MNPs have also demonstrated adverse reactions. There is evidence that MNPs and their additives could be involved in the pathogenesis of non-alcoholic fatty liver disease (NAFLD), which has become the predominant cause of chronic liver injury (Auguet et al., 2022) (Li et al., 2022). Other authors have also described alterations at the transcriptional level of proteins involved in the synthesis and transport of bile acids in the liver of mice exposed to PS MNPs (Jin et al., 2019), which is associated with epigenetic changes and transgenerational effects of exposure to MNPs (López de las Hazas et al., 2022), whose potential consequences in the early stages of life, as well as a causal relationship with obesity in humans, have not yet been evaluated. The distribution of PE NPs in the white adipose tissue of mice has recently been described for the first time, and it has been suggested that chronic oral exposure to NPs at concentrations relevant to dietary exposure (3 and 223 µg/kg b.w.) alters fasting-induced lipid mobilisation in obese mice and, subsequently, contributes to increased adipocyte size and lipid accumulation in the liver (Shiu et al., 2022).

Other metabolic disorders recorded after exposure to MNPs are associated with alterations of the intestinal microbiota (Jiménez-Arroyo et al., 2023). It is well known that the loss of diversity of the intestine microbiota, known as intestinal dysbiosis, is related to local effects (digestive) as well as systemic (in other organs and tissues), due to the alteration of physiological homoeostasis, causing metabolic diseases. Dysbiosis of the intestinal microbiota is a common effect of MNPs, demonstrated in numerous studies in both vertebrates and invertebrates, including mammals (Jin et al., 2019) (Zhao et al., 2021), as well as epidemiological studies in subjects exposed to MNPs for extended periods (Liu et al., 2022). The intestine microbiota is considered an indispensable organ that interacts with host cells during metabolic processes. The exposure to different types of polymers, forms and sizes (mainly PS, PE and PET), provokes changes in the balance of commensal populations, allowing pathogens overgrowth. Specifically, a change in the Firmicutes/Bacteroidetes ratio has been evidenced, the increase of which is associated with obesity (Turnbaugh et al., 2006). Using *in vitro* gastrointestinal systems representative of the physiological conditions of

the human intestine, it has been shown that pet MPs at realistic daily doses of human intake, in addition to causing a dysfunction of the composition of the intestinal microbiota, can also undergo biotransformations by the bacteria of the intestine, giving rise to smaller and, therefore, more bioavailable particles (Tamargo et al., 2022), and that the bacteria of the microbiota can release at the colonic level some additives associated with the MPs, such as phthalates (Yan et al., 2022b), on which different obesity-inducing effects have been described. To date, there are no epidemiological studies that have investigated the relationship between exposure to microplastics and obesity, although its additives or associated chemical contaminants such as bisphenols, phthalates and organotin compounds.

12.4 Summary of scientific evidence and comments

The study of the effects of MNPs particles on human health is an emerging research topic. Although recent results so far do not allow identifying an association between MNPs intake and obesity, accumulated evidence in rodents on the effects of MNPs on glucose and lipid metabolism, and evidence of accumulation of these particles in the human body, suggests the need for further research in this field to assess both the potential obesogenic effects of short- and long-term exposures to MNPs and their constituent substances. Especially, it is important to note that some of the better known obesogens discussed in other sections of this report contaminate different MNPs. On the other hand, several lines of evidence suggest the possible involvement of the MNPs that humans ingest and/or inhale, in the pathogenesis of metabolic diseases such as NAFLD, and probably also through an effect on the modulation of the intestinal microbiota and its metabolic function, and the intestine-liver axis, although there is a lack of studies on humans.

13. Other compounds with potential obesogenic activity

There are other compounds whose obesogenic activity is under study and of which there is less scientific evidence such as neonicotinoid insecticides, chlorpyrifos, permethrin, tolylfluanid fungicide and parabens among others (Hu et al., 2013) (Heindel et al., 2022). These compounds have been studied *in vitro*, in *vivo* and in some epidemiological cases pointing to a possible obesogenic effect (Park et al., 2013) (Sun et al., 2016) (Chen et al., 2018) (Kim et al., 2018) (Xiao et al., 2018) (Ruiz et al., 2019) (Blanco et al., 2020) (Guardia-Escote et al., 2020) (Monteagudo et al., 2021). More work is needed to investigate the effect of these compounds and others with possible obesogenic activity in different models and systems.

Conclusions of the Scientific Committee

The results of the *in vivo* and *in vitro* studies considered demonstrate that BPA and analogues, phthalates, TBT, PCBs, dioxins, the organochlorine pesticide DDT and its metabolite DDE, flame retardants and PFAs act as obesogens, although in some cases the evidence is weak. Some epidemiological studies evaluated reinforce the hypothesis of a relationship between exposure to these compounds and obesity, especially when such exposure takes place during intrauterine life and early childhood. However, it is necessary to conduct more studies in humans, standardising bio-

markers of exposure and effect to predict and evaluate their obesogenic capacity, and the possible transmission of the effect to other generations through epigenetic mechanisms.

In the case of metals and triclosan, the contradictory data shown in different studies invite more work to elucidate their role as obesogens. There are also very few studies investigating the role of MNPs as obesogens. However, the results of animal trials suggest the need for further investigation in this field. In addition, more work is needed to investigate the effect in different models and systems of compounds of suspected obesogenic activity such as some insecticides, fungicides and parabens, among others.

Although there is evidence to support the conclusions on the obesogenic activity of some substances, it is necessary to reach a consensus in the scientific community in the near future about the effect that a compound must have to be considered obesogenic, to make a list of substances with possible obesogenic activity and to develop a battery of tests to study them.

On the other hand, considering the scientific evidence analysed in this report, there are important knowledge gaps concerning the effects of dietary exposure to obesogens.

In short, the biological effects and mechanisms of action of obesogens should be studied in depth. It is also necessary to investigate the effect of exposure to the mixture of obesity-causing substances found in food along with those from other sources of exposure. Likewise, studies are needed to consider the interaction of exposure to multiple obesogens and other risk factors in obesity, such as diet, exercise, inflammation, disruption of circadian rhythms, oxidative stress, mitochondrial dysfunction, mealtime, and regulation of appetite and satiety. These interactions can be critical in understanding obesogens in humans. In addition, more scientific works that consider sexual dimorphism in the effect that some obesogens may present is indispensable.

Once all relevant evidence is available, there should be coordination and communication between scientists, clinicians and national and international regulatory agencies to develop a comprehensive and efficient strategy for the implementation of risk management measures to minimize as much as possible exposure to these substances.

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