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Review article

Bisphenol A and its analogues: A comprehensive review to identify and prioritize effect biomarkers for human biomonitoring

Vicente Mustieles[a,b,c,1,*], Shereen Cynthia D'Cruz[d,1], Stephan Couderq[e,1], Andrea Rodríguez-Carrillo[a], Jean-Baptiste Fini[e], Tim Hofer[f], Inger-Lise Steffensen[f], Hubert Dirven[f], Robert Barouki[g], Nicolás Olea[a,b,c], Mariana F. Fernández[a,b,c,2,*], Arthur David[d,2,*]

[a] University of Granada, Center for Biomedical Research (CIBM), Spain
[b] Instituto de Investigación Biosanitaria (ibs. GRANADA), Spain
[c] Consortium for Biomedical Research in Epidemiology & Public Health (CIBERESP), Spain
[d] Univ Rennes, EHESP, Inserm, Irset (Institut de recherche en santé, environnement et travail) – UMR_S 1085, F-35000 Rennes, France
[e] Evolution des Régulations Endocriniennes, Département "Adaptation du Vivant", UMR 7221 MNHN/CNRS, Sorbonne Université, Paris 75006, France
[f] Section of Toxicology and Risk Assessment, Norwegian Institute of Public Health, P.O. Box 222 Skøyen, NO-0213 Oslo, Norway
[g] University Paris Descartes, ComUE Sorbonne Paris Cité, Paris, France. Institut national de la santé et de la recherche médicale (INSERM, National Institute of Health & Medical Research) UMR S-1124, Paris, France

Abbreviations: **AO**, adverse outcome; **AOP**, adverse outcome pathway; **ACR**, albumin-to-creatinine ratio; **AD**, androstenedione; **AhR**, aryl hydrocarbon receptor; **ALT**, alanine aminotransferase; **AMH**, anti-Müllerian hormone; **AP**, alkaline phosphatase; **AR**, androgen receptor; **AST**, aspartate aminotransferase; **BEX2**, brain expressed X-linked 2; **BDNF**, brain-derived neurotrophic factor; **BPA**, bisphenol A; **BRCA1**, breast cancer 1; **CaMKII**, calcium/calmodulin-dependent kinase II; **CMHS**, Canadian measures health survey; **COMT**, catechol O-methyltransferase; **CpG**, 5′—cytosine—phosphate—guanine—3′; **CREB**, cAMP response element-binding protein; **CRP**, c-reactive protein; **DHEA-S**, dehydroepiandrosterone sulfate; **DHT**, dihydrotestosterone; **DNA**, deoxyribonucleic acid; **E1**, estrone; **E2**, 17β-estradiol; **E3**, estriol; **EDCs**, endocrine-disrupting chemicals; **ERR**, estrogen related receptor; **ER**, estrogen receptor; **FAI**, free androgen index; **FSH**, follicle stimulating hormone; **FT**, free testosterone; **FT3**, free triiodothyronine; **FT4**, free thyroxine; **GDNF**, glial cell-derived neurotrophic factor; **GnRH**, gonadotrophin releasing hormone; **GGT**, gamma glutamyl transpeptidase; **GSH**, glutathione, reduced form; **HbA1c**, glycated hemoglobin; **HBM**, human biomonitoring; **HBM4EU**, European Human Biomonitoring Initiative; **HDL-C**, high-density lipoprotein cholesterol; **HNE-MA**, 4-hydroxy-2-nonenal-mercapturic acid; **HOXA10**, homeobox A10; **HOMA-B**, homeostasis model assessment of beta-cell function; **HOMA-IR**, homeostasis model assessment for insulin resistance; **HP**, hypothalamus-pituitary; **HPA**, hypothalamus–pituitaryadrenal; **HPLC**, high performance liquid chromatography; **HPT**, hypothalamus-pituitary-thyroid; **hs-CRP**, high-sensitivity c-reactive protein; **IgE**, immunoglobulin E; **IL**, interleukin; **INHB**, inhibin B; **INSL3**, insulin-like peptide 3; **KE**, key event; **KiSS**, kisspeptin; **LD**, lactate dehydrogenase; **LDL-C**, low-density lipoprotein cholesterol; **LH**, luteinizing hormone; **LINE-1**, long interspersed element-1; **LTP**, long-term potentiation; **LTRs**, long terminal repeats; **MDA**, malondialdehyde; **MIE**, molecular initiating event; **MoA**, mode of action; **NHANES**, National Health and Nutrition Examination Survey; **NIS**, sodium/iodide symporter; **NMDARs**, glutamate N-methyl-D-aspartate receptors; **NRs**, nuclear receptors; **NRC**, National Research Council; **PCOS**, polycystic ovary syndrome; **PlGF**, placental growth factor; **PBMCs**, peripheral blood mononuclear cells; **PREG**, pregnenolone; **PRL**, prolactin; **PXR**, pregnane X receptor; **P4**, progesterone; **RHs**, reproductive hormones; **RNA**, ribonucleic acid; **ROS**, reactive oxygen species; **sFlt1**, soluble fms-like tyrosine kinase-1; **SHBG**, sex hormone-binding globulin; **SP4**, specific protein 4; **STAT3**, signal transducer and activator of transcription 3; **SULT2A1**, sulfotransferase family 2A member 1; **TBA2-MDA**, thiobarbituric acid-malondialdehyde; **TC**, total cholesterol; **TG**, triglycerides; **THs**, thyroid hormones; **TNF-α**, tumor necrosis factor alpha; **TPOab**, thyroid peroxidase autoantibodies; **TSH**, thyroid-stimulating hormone; **TSLP**, thymic stromal lymphopoietin; **TSP50**, testis-specific protease-like protein 50; **TT**, total testosterone; **TT3**, total triiodothyronine; **TT4**, total thyroxine; **T2DM**, type 2 diabetes mellitus; **U.S.**, the United States of America; **WHO**, World Health Organization; **8OHdG**, 8-hydroxy-2′-deoxyguanosine; **8-isoprostane**, 8-*iso*-prostaglandin F2α

* Corresponding authors at: University of Granada, Center for Biomedical Research (CIBM), Spain (V.Mustieles); Instituto de Investigación Biosanitaria (ibs. GRANADA), Spain (M.F. Fernández); and Univ Rennes, EHESP, Inserm, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, F-35000, Rennes, France (A. David).

E-mail addresses: vmustieles@ugr.es (V. Mustieles), marieta@ugr.es (M.F. Fernández), arthur.david@ehesp.fr (A. David).

[1] Authors contributed equally.

[2] Co-last authors.

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ABSTRACT

Human biomonitoring (HBM) studies have demonstrated widespread and daily exposure to bisphenol A (BPA). Moreover, BPA structural analogues (e.g. BPS, BPF, BPAF), used as BPA replacements, are being increasingly detected in human biological matrices. BPA and some of its analogues are classified as endocrine disruptors suspected of contributing to adverse health outcomes such as altered reproduction and neurodevelopment, obesity, and metabolic disorders among other developmental and chronic impairments. One of the aims of the H2020 European Human Biomonitoring Initiative (HBM4EU) is the implementation of effect biomarkers at large scales in future HBM studies in a systematic and standardized way, in order to complement exposure data with mechanistically-based biomarkers of early adverse effects. This review aimed to identify and prioritize existing biomarkers of effect for BPA, as well as to provide relevant mechanistic and adverse outcome pathway (AOP) information in order to cover knowledge gaps and better interpret effect biomarker data. A comprehensive literature search was performed in PubMed to identify all the epidemiologic studies published in the last 10 years addressing the potential relationship between bisphenols exposure and alterations in biological parameters. A total of 5716 references were screened, out of which, 119 full-text articles were analyzed and tabulated in detail. This work provides first an overview of all epigenetics, gene transcription, oxidative stress, reproductive, glucocorticoid and thyroid hormones, metabolic and allergy/immune biomarkers previously studied. Then, promising effect biomarkers related to altered neurodevelopmental and reproductive outcomes including brain-derived neurotrophic factor (BDNF), kisspeptin (KiSS), and gene expression of nuclear receptors are prioritized, providing mechanistic insights based on *in vitro*, animal studies and AOP information. Finally, the potential of omics technologies for biomarker discovery and its implications for risk assessment are discussed. To the best of our knowledge, this is the first effort to comprehensively identify bisphenol-related biomarkers of effect for HBM purposes.

1. Introduction

Bisphenol A (BPA) is a synthetic high production monomer used in polycarbonate plastics and epoxy resins in a wide range of consumer products. These include for instance canned food and beverages, plastic bottles, food containers, toys, thermal receipts, and medical equipment among many other applications (Calafat et al., 2009; Cao et al., 2009; Carwile et al., 2009; Ehrlich et al., 2014; Fleisch et al., 2010; Iribarne-Durán et al., 2019; Molina-Molina et al., 2019; Vandenberg et al., 2007). More recently, BPA has even been detected in infants' socks, highlighting the novel role of textiles as potential source of bisphenol exposure (Freire et al., 2019). Although diet is one of the predominant sources of BPA exposure in the general population due to the leaching of BPA from packaging materials and can liners into food and beverages (Buckley et al., 2019; Vandenberg et al., 2010), other sources and routes also contribute to human exposure (Freire et al., 2019; Molina-Molina et al., 2019; Morgan et al., 2018). Indeed, non-dietary sources (e.g. dermal and inhalation) have been proposed to be of equal or even higher toxicological relevance than dietary sources based on markedly different toxicokinetics (Liu and Martin, 2017; von Goetz et al., 2017).

Assessing human exposure to BPA is challenging, mainly due to its short biological half-life and rapid excretion. Furthermore, problems related to external contamination during sampling and/or analytical processes have been reported in some studies (Teeguarden et al., 2016; Ye et al., 2013). Biomonitoring studies have assessed BPA in blood plasma, serum and tissues; however, the analysis of total urinary BPA (i.e. free BPA and phase II conjugates) after enzymatic deconjugation is widely recognized as the standard approach (Calafat et al., 2015). Thus, HBM studies have demonstrated widespread and daily exposure to BPA, detecting urinary BPA in more than 90% of the general European and US populations at low concentrations (Becker et al., 2009; Calafat et al., 2008). The advantages of urine as exposure matrix include its non-invasiveness and the possibility to collect repeated samples over time, which is important for a reliable assessment of non-persistent chemicals with short biological half-lives and episodic exposure patterns (Vernet et al., 2019). However, urinary BPA concentrations do not directly inform about bioactive concentrations in specific tissues or internal levels, nor differentiate among exposure routes. Hence, some studies have suggested that measurements in other biological matrices would also be convenient under specific circumstances (Stahlhut et al., 2016). Additionally, recent data requiring further confirmation suggests that BPA exposure assessment using indirect analytical techniques involving enzymatic deconjugation could underestimate human urinary BPA concentrations depending on the protocol used (Gerona et al., 2019). These inherent limitations related to BPA exposure assessment in HBM studies must be considered when interpreting exposure-health associations.

BPA is a known endocrine disrupting chemical (EDC) that can interfere with hormonal balance even at low doses (Rubin, 2011). Its mechanisms of action are particularly complex since BPA can bind not only to nuclear and membrane estrogen receptors but also to thyroid, glucocorticoid, and peroxisome proliferator-activated receptors. It can also interact with steroidogenic enzymes, among other molecular targets (Acconcia et al., 2015; Mustieles et al., 2018a; Rubin, 2011; Wetherill et al., 2007). Additionally, BPA has been shown to exert epigenetic modifications (e.g. altered DNA methylation) that could partially explain BPA effects on various health endpoints (Ferreira et al., 2015; Kundakovic and Champagne, 2011). Taken together, this biological promiscuity might explain the pleiotropic effects exerted by BPA on behavior, reproduction, and metabolism in both experimental animals (Nesan et al., 2018; Peretz et al., 2014; Wassenaar et al., 2017) and human populations (Chevalier and Fénichel, 2015; Mustieles et al., 2015; Peretz et al., 2014). Other health outcomes suspected of being affected by BPA exposure include hormone-dependent cancers, the immune system and developmental diseases (Bansal et al., 2018; Murata and Kang, 2018; Rochester, 2013). Although associations found in human populations cannot demonstrate causality, BPA effects on different systems and organs are supported by an extensive body of experimental evidence. For some endpoints such as reproduction and behavior, the epidemiological findings are also increasingly consistent (Mustieles et al., 2018a, 2015; Peretz et al., 2014).

BPA has recently been classified as a reproductive toxicant and a substance of very high concern by the European Chemicals Agency (ECHA, 2016, 2017). However, most BPA replacements are structural analogs such as bisphenol S (BPS) and bisphenol F (BPF), which also show hormonal activity (Molina-Molina et al., 2013; Rochester and Bolden, 2015) and are increasingly detected in human urine (Yang et al., 2014b; Ye et al., 2015). Many other bisphenol analogues, including bisphenol AF (BPAF), bisphenol AP (BPAP), bisphenol Z (BPZ), and bisphenol B (BPB) have also been shown to exert estrogenic activities (Chen et al., 2016; Mesnage et al., 2017; Moreman et al., 2017), with the exception of tetramethyl bisphenol F (Soto et al., 2017). Since

recent animal studies have shown that exposure to bisphenol analogues such as BPS, BPF and BPAF induce a similar pattern of neurobehavioral disruption as BPA (Rosenfeld, 2017), there is an urgent need for new monitoring approaches that can timely address the potential risks posed by bisphenol analogues in order to avoid regrettable substitutions of BPA and other environmental chemicals.

The European Human Biomonitoring Initiative (HBM4EU) represents a joint effort of 28 countries and the European Commission, co-funded by Horizon 2020. Its main aim is to coordinate and advance HBM in Europe in a standardized way to provide evidence for policy-making. The HBM4EU consortium identified several critical questions concerning bisphenols, which include the identification of bisphenol-related effect biomarkers and their mechanistic pathways following the adverse outcome pathway (AOP) framework. Effect biomarkers are measurable biological changes helpful for establishing dose–response and mechanistic relationships. By providing a link between exposure, internal dose and early health impairment, they could be extremely useful in order to improve HBM and risk assessment of chemicals with a very short half-life (Decaprio, 1997) (Fig. 1). Based on the WHO and the Committee on Human Biomonitoring for Environmental Toxicants (IPCS-WHO, 1993; NRC, 2006), effect biomarkers are defined as "a measurable biochemical, physiologic, behavioral, or other alteration in an organism that, depending on the magnitude, can be recognized as associated with an established or possible health impairment."

Fig. 1 presents a simplified unidirectional conceptualization of the exposure-disease continuum for practical purposes. However, it is worth noting that real-life scenarios are much more complex and dynamic. The development of an adverse effect in humans will depend on the route of exposure to BPA and the internal dose at the target organ, the critical window of exposure, individual susceptibility, as well as potential non-monotonic dose-responses together with adaptive mechanisms and feedback regulations (Mustieles and Arrebola, 2020). An important characteristic that complicates the evaluation of BPA effects in both experimental toxicology and human settings is the probable existence of non-monotonic dose–response relationships, also typical of endogenous hormones (Hill et al., 2018; Vandenberg et al., 2019, 2012). In relation to biomarkers of effect, different biomarker profiles could be expected for those exposed to the highest levels compared to other exposure ranges, as well as for occupationally-exposed subjects compared to the general population. Thus, the shape of exposure-health associations should be evaluated *a priori*, without assuming the existence of linearity across all exposure ranges.

Based on the needs identified, this work aimed to: i) conduct a comprehensive review of the literature to create an inventory of existing effect biomarkers used in epidemiologic studies related to bisphenols exposure and specific health endpoints of concern; ii) prioritize the most relevant biomarkers of effect for HBM purposes; iii) provide relevant mechanistic and/or AOP information to improve the interpretation of biomarker data; and iv) identify gaps in knowledge and potential novel effect biomarkers to be investigated in future biomonitoring programs. To the best of our knowledge, this is the first effort to identify the best epidemiological effect biomarkers for BPA and its analogues for HBM purposes.

2. Methods

2.1. Literature search methodology

This comprehensive review covered all scientific publications available in the PubMed/MEDLINE database from January 2008 up to January 2018 with the aim of identifying effect biomarkers linked to bisphenol exposure and human adverse health effects. To decomplexify the very large amount of references found and prioritize the most relevant effect biomarkers, three general steps were followed:

First, relevant search terms including both MeSH and non-MeSH terms (Suppl. Table 1) for both the exposure (bisphenols) and selected health endpoints were selected. To cover as much information as possible, the term "bisphenol" was chosen as the key search term for exposure. Six health endpoints were *a priori* chosen according to their relevance for BPA-related human health and HBM4EU objectives: i) neurodevelopment, ii) reproductive diseases, iii) endocrine diseases, iv) obesity, cardiovascular and metabolic disorders, v) allergies and immunological diseases and vi) cancer. Afterwards, boolean operators 'AND' and 'OR' were used to combine search terms (Suppl. Table 1). Several PubMed filters were employed to gain precision: a) "Full-text" articles and b) published in the last "10 years". As a result of this exploratory search, 5716 potential references were found (Suppl. Fig. 1).

A screening procedure of the abovementioned 5716 abstracts was performed to identify relevant articles reporting effect biomarker information for each outcome of interest. At least two researchers participated in the selection of abstracts for each health endpoint. The following exclusion criteria were applied: a) articles with only exposure

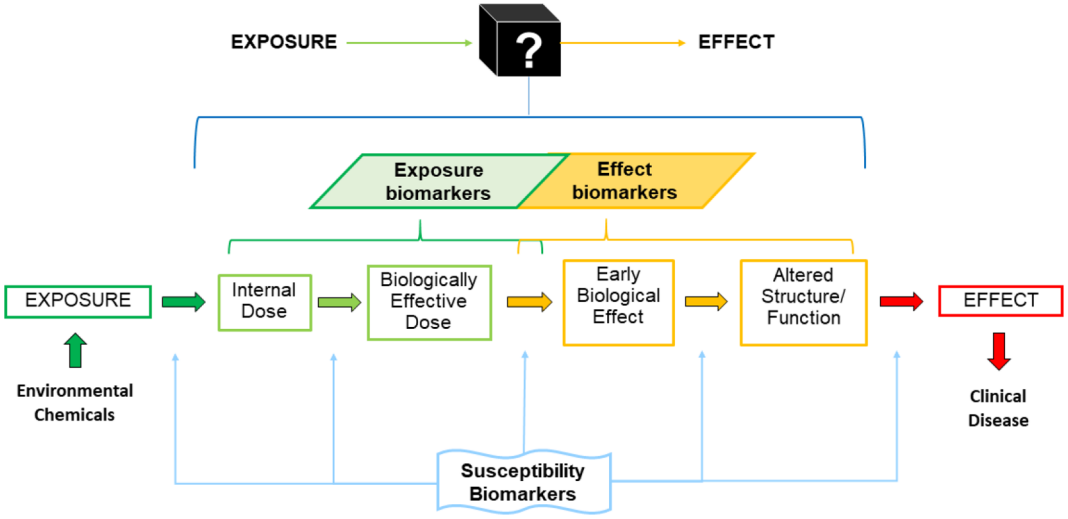


Fig. 1. Conceptual pathway representing the continuum between environmental chemical exposure and clinical disease (adaptation of the National Research Council biomarker paradigm identifying concrete stages in the exposure-disease continuum). Exposure biomarkers measure the actual absorbed dose ("internal dose") and active dose at the putative target organ/tissue ("biologically effective dose"). Effect biomarkers measure early molecular or biochemical/cellular responses in target or non-target tissues ("early biological effect"), functional or structural changes in affected cells or tissues ("altered structure/function"), or actual clinical disease. Susceptibility biomarkers help to identify individuals with genetically mediated predisposition to xenobiotic-induced toxicity (Adapted from De Caprio, 1997).

data, b) non-original research articles, and c) articles with only experimental or *in vivo* studies. Then, duplicate references were removed. Suppl. Fig. 2 shows the flow-chart of the selection process.

Finally, all the information provided by each of the 119 selected studies was collected, analyzed, synthetized and tabulated (Suppl. Tables 2-9). We reported study quality parameters such as study design; characteristics of the population including sample size; exposure assessment (biological matrix, number of samples analyzed, methods followed and quality measures); the effect biomarkers measured in each biological matrix, and the analytical method used; as well as the main results and conclusions. Throughout this in-depth screening, we additionally considered criteria such as the feasibility of the biomarker together with its specificity, sensitivity, and reliability, and if a potential mode of action (MoA) and/or adverse outcome pathway (AOP) were previously described.

After conducting the review and analyzing its results, some gaps in knowledge were identified. Therefore, a fourth post-hoc step was performed by hand-search to gather AOP information (https://aopwiki.org/) and specific BPA mechanistic studies (PubMed database) that may experimentally support the implementation of selected promising novel effect biomarkers found in this work [brain-derived neurotrophic factor (BDNF), kisspeptin (KiSS) and gene expression of nuclear receptors].

2.2. Classification of effect biomarkers in the AOP context

After analyzing all references, effect biomarkers were classified into two main categories based on their level of biological organization: molecular effect biomarkers and cellular/biochemical effect biomarkers. This classification was based mainly on the AOP framework. AOPs have been developed recently and are conceptual constructs that integrate existing knowledge on the linkage between a direct molecular initiating event (MIE), through its associated key events (KEs) until the development of an adverse outcome (AO) at a biological level of organization relevant to risk assessment (Ankley et al., 2010) (see Fig. 2). Within this classification, molecular effect biomarkers include biological markers such as epigenetic modifications (e.g., DNA methylation) and changes in gene expression. These molecular effect biomarkers are more likely to coincide with early KEs or even molecular initiating events (MIEs) in the AOP framework, meaning that these biomarkers are potentially closer to the exposure. The main limitation is that their predictive potential for adverse effects is most of the time unknown, in particular for epigenetic biomarkers. In contrast, biochemical or cellular biomarkers (e.g., hormones, insulin and glucose levels, etc.) are generally closer to the phenotype and are therefore more likely to be representative of late KEs in the AOP framework. The main strength of biochemical/cellular biomarkers is their predictive potential for disease; however, they may be less specific. Overall, the combination of both molecular and biochemical effect biomarkers, when substantiated by an AOP-like conceptualization of the *in vitro* and *in vivo* evidence, appears as an optimal approach for improving the causal understanding of exposure-disease relationships in HBM studies.

3. Results and discussion

3.1. Inventory and description of existing effect biomarkers identified in human studies

3.1.1. Molecular effect biomarkers

Molecular effect biomarkers identified in this literature search include epigenetic and gene expression biomarkers (Suppl. Table 2) as well as oxidative stress markers (Suppl. Table 3), which are summarized in Table 1.

3.1.1.1. Epigenetic biomarkers. Epigenetics refers to heritable alterations in gene expression that do not involve alterations in the DNA sequence. The main epigenetic regulators include DNA methylation, histone modifications, and microRNAs. Overall, epigenetic markers are stable biomarkers that can be transmitted to subsequent generations and studies have already shown that modifications of DNA methylation patterns can potentially serve as relevant effect biomarkers for a wide range of environmental contaminants such as dioxins, plasticizers, pesticides, and hydrocarbons (Manikkam et al., 2012).

A variety of epigenetic markers associated with exposure to bisphenols have been inventoried through this literature search. These epigenetic markers were related to different health outcomes such as reproduction, neurodevelopment, obesity and metabolic disorders. Among the retrieved papers, eight studies analyzed hypo- or hypermethylation of specific candidate genes, one study focused on DNA hydroxymethylation, and two studies investigated microRNA alterations (Suppl. Table 2).

Regarding hypo- or hyper DNA methylation markers, associations between urinary BPA concentrations and alterations in the methylation patterns of DNA isolated from saliva of genes involved in immune function, transport activity, metabolism, and caspase activity were observed in pre-pubescent girls from Egyptian rural (n = 30) and urban

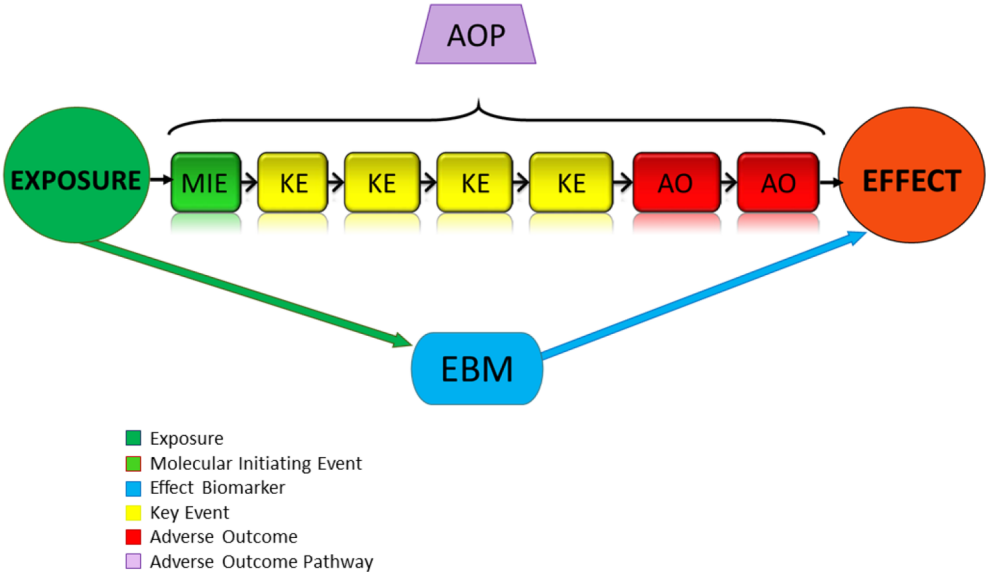


Fig. 2. Visualization of the AOP network and the analogy between intermediate steps and effect biomarkers (EBM) of interest for HBM. Both early KEs (i.e., early biological changes such as epigenetic modifications and altered gene expression) and late KEs (i.e., altered structure or function markers such as sexual hormones and glucose/insulin) in a given AOP have the potential to be assessed or implemented as EBM in epidemiologic studies.

Table 1
Inventory of bisphenol-related epigenetic and oxidative stress effect biomarkers identified in HBM studies.

Biomarkers	Matrix	Health endpoint	Number of studies	Strengths	Limitations	Conclusions
				Epigenetic/Gene expression Biomarkers [a]		
DNA methylation of BDNF Region IV	Blood	Neurodevelopmental disorders	1 (Table S2)	DNA methylation is stable over time compared to gene expression or circulating protein levels, which are subjected to short-term variations. BDNF pathway alteration can affect long-term memory, learning, and depression and anxiety disorders. In mice, DNA methylation of BDNF in hippocampus is correlated with blood methylation.	DNA methylation regions should be carefully selected, mainly the promoter regions, so the status of DNA methylation is related with its gene expression.Although the DNA methylation status of BDNF in blood is a promising biomarker for brain function, its predictive potential and role is not fully understood.	Neurotrophins like BDNF constitute potential effect biomarkers of brain function for bisphenols. Molecular/biochemical biomarkers of brain function constitute an important knowledge gap. The potential of this novel biomarker warrants further research at different biological levels (DNA, RNA, protein…) in HBM studies.
Gene expression of nuclear receptors (ERs, ERRs, AR, TRs, AhR, PPARs)	Blood and Semen	Reproduction Metabolic disorders	2 (Table S2)	Gene expression of nuclear receptors and other targets in PBMCs could be a surrogate of their gene expression in target organs, providing relevant data on potential mechanisms of action.	In most cases, the predictive potential for a given disease is unknown. Notwithstanding, emerging data is supporting their suitability for specific health endpoints.	Although their predictive potential is uncertain, when combined with other related molecular or biochemical effect biomarkers, gene expression markers in PBMCs can help to identify potential mechanisms and increase the biological plausibility of epidemiologic associations.
KiSS gene expression	Placenta	Pregnancy adverse outcomes/ Reproduction Disorders	1(Table S2)	*KISS1* is a major regulator of puberty onset and other reproductive functions. Kisspeptin neuron stimulation is an essential event upstream of GnRH pulse release from the HPG axis, and BPA has been shown to adversely affect kisspeptin neuronal system. Therefore, *KISS1* expression could serve as an early indicator of reproductive dysfunctions associated with BPA exposure.	Kisspeptin carries out a variety of physiological functions from reproduction to metabolism. So precisely identifying the health issue associated with *KiSS* deregulation may be difficult.	Kisspeptin gene dysregulation could be a very early indicator of HPG axis dysfunction and its downstream hormonal events associated with reproduction. Since BPA is a recognized reprotoxicant, assessment of *KISS1* in combination with other biomarkers could help to map the key events underlying BPA's adverse reproductive effects.
Sperm epigenetic marks (LINE-1 methylation and 5-hydroxy-methylcytosine)	Sperm	Reproduction Disorders	1(Table S2) 1(Table S2)	LINES are a group of long terminal repeats and their methylation status could serve as a surrogate measure of global DNA methylation. 5-hydroxymethylcytosine (5hmC), also called as DNA hydroxymethylation, is an intermediate step in DNA demethylation process, and is a relatively stable epigenetic mark. 5hmc can associate with chromatin regulatory proteins and thus could regulate gene transcription.	A limitation of assessing LINEs is their lack of specificity. LINEs are repeat elements, and mapping their genome location would be difficult. Although a global loss of 5hmC has been observed in some cancers, its physiological role still remains elusive.	Semen constitutes a non-invasive sample that can provide effect data at different levels of organization: from cell counts and functional aspects, to seminal hormones, and sperm epigenetic and gene expression markers. Future studies should explore the implementation of molecular epigenetic markers together with more classical semen parameters.
				Oxidative stress biomarkers [a]		
8OHdG and 8-isoprostane	Urine	Oxidative stress	11(8OHdG) and 2 (8-isopr.)(Table S3)	Both markers are easy to measure in urine, which is preferred over serum. 8OHdG is a marker of DNA damage, and 8-isoprostane of lipid peroxidation. They are predictive of diverse chronic diseases including metabolic syndrome, cardiovascular disease and cancers.	The biggest limitation is the lack of specificity for a given exposure or a specific tissue/ organ. Since these markers can be affected by dietary patterns, future studies should consider diet intake. Considerable inter- and intra-day variations, which can be minimized by collecting repeated urine samples. Additionally, there is a small risk of artefactual formation/degradation during sample processing.	In general, positive associations have been reported with 8OHdG in relation to BPA, and also other structural analogues. Although there are fewer studies evaluating 8-isoprostane, positive associations are also dominant. These oxidative stress markers, although not specific to a unique health endpoint, are able to capture disruptions at different levels of biological organization. Thus, they have been demonstrated useful in mediation analyses between exposure biomarkers and health endpoints. These markers should be corrected for urinary dilution. Overall, their use in combination with other more specific markers should be encouraged.

(*continued on next page*)

Table 1 (*continued*)

Biomarkers	Matrix	Health endpoint	Number of studies	Strengths	Limitations	Conclusions
MDA	Urine	Oxidative stress	6 (Table S3)	Several positive associations in relation to BPA exposure have been reported. MDA is specific for lipid peroxidation.	Risk of artefactual generation during preparatory steps involving excessive heating prior to analysis. Not BPA or organ specific.	Although assessment of MDA is preferred in urine than serum, the possibility of artefactual generation still remains. The first methodological option is a HPLC separation prior to UV or fluorescence analysis of the TBA_2-MDA chromophore. Urinary HNE-MA constitutes another promising marker of lipid peroxidation that was recently associated with bisphenol analogues.
3-NO_2Tyr	Plasma	Nitrosative stress	1(Table S3)	The study that investigated this marker in relation to human prenatal BPA exposure was an interspecies comparison. Thus, it is experimentally supported.	Lack of specificity for a given exposure or a specific tissue/organ.	A positive association between BPA and 3-NO_2Tyr (but not 3-ClTyr and diTyr) was found in plasma from pregnant mothers and umbilical cords. This was supported by similar effects in sheep and rodents. Although limited data is available, future studies may evaluate markers of nitrosative stress, especially in cord blood in relation to maternal prenatal BPA exposure.

Abbreviations: AhR (aryl hydrocarbon receptor); AR (androgen receptor); BDNF (brain-derived neurotrophic factor); ERs (estrogen receptors), ERRs (estrogen-related receptors), KiSS (kissepti n); LINE (long interspersed nuclear elements); MDA (malondialdehyde acid); PPARs (peroxisome proliferator-activated receptors), TRs (thyroid receptors); 8OHdG (8-hydroxy-2′-deoxyguanosine); 3-NO_2Tyr (3-nitrotyrosine).

[a] Effect biomarkers of lower interest or measured in invasive matrices are not reported in the table but in the text.

areas (n = 30) using untargeted genome-wide profiling (Kim et al., 2013). More specifically, homeobox A10 (HOXA10) involved in embryo morphogenesis; breast cancer 1 (BRCA1), involved in DNA transcription and repair; and brain expressed X-linked 2 (BEX2) associated with estrogens and cell cycle, were found to be hypo-methylated. Another study reported alterations in DNA methylation in relation to BPA exposure assessed in fetal liver tissue and signal transducer and activator of transcription 3 (STAT3) also evaluated in fetal liver samples (n = 50) (Weinhouse et al., 2015). STAT3 signaling is associated with inflammatory liver cancer (Svinka et al., 2014) and STAT3 methylation has been proposed as a possible biomarker for liver tumor risk (Weinhouse et al., 2015). Increased site-specific methylation of COMT, a gene that encodes for catechol-O-methyltransferase involved in the metabolism of catecholamines and SULT2A1, a phase II metabolism enzyme, was also observed in human fetal liver in response to higher BPA concentrations (Nahar et al., 2014). Hanna et al. (2012) reported an inverse correlation between serum BPA concentrations and altered testis-specific protein 50 (TSP50) gene methylation levels in the blood of women (n = 35) who were undergoing *in vitro* fertilization. Although the exact function of TSP50 is not fully elucidated, an increased expression of TSP50 due to loss of its normal methylation was observed in breast cancer epithelial cells, but not in normal breast tissues (Shan et al., 2002).

A recent study using data from the Columbia Center for Children's Environmental Health (CCCEH) cohort showed that higher prenatal urinary BPA concentrations during the third trimester of gestation were prospectively associated with altered cord blood DNA methylation of BDNF Exon IV at two CpG sites in a sex-specific manner (n = 41 females, n = 40 males), and these effects were more pronounced in boys compared to girls (Kundakovic et al., 2015). Importantly, prenatal BPA was previously associated with behavior problems in 198 children from this same cohort (Perera et al., 2012). This study was considered of high quality based on its prospective design, robust exposure and effect measurements, and the validation of its results using a rodent model investigating BDNF DNA methylation in both brain tissue and whole blood in response to BPA dosing (Kundakovic et al., 2015). BDNF is a member of the neurotrophin family and is a key regulator of neuronal synaptic plasticity. BDNF is considered a biomarker specific for neurobehavioral disorders as it is involved in the pathogenesis of various psychiatric ailments such as depression, anxiety, schizophrenia and bipolar disorder (Autry and Monteggia, 2012). For instance, altered BDNF levels have been associated with attention deficit, cognitive skill decline and behavioural defects in children (Cubero-Millán et al., 2017; Yeom et al., 2016). From a neurodevelopmental point of view, DNA methylation of BDNF Exon IV constitutes one of the most promising biomarkers identified for BPA.

In another study following a targeted analysis, long interspersed nuclear elements (LINE) were reported to be hypo-methylated in the spermatozoa of Chinese factory workers exposed to BPA (n = 77) compared to non-exposed workers (n = 72) (Miao et al., 2014). LINEs are a group of non-long terminal repeat retrotransposons that comprises approximately 17% of the human genome and are normally heavily methylated in order to prevent genome instability. It is also considered to be a surrogate marker of global DNA methylation. Experimental studies conducted on human fetal liver samples (n = 18) found an association between BPA concentrations in liver and hypomethylation of LINEs, long terminal repeat (LTRs), satellite repeats and DNA elements (Faulk et al., 2016). Moreover, an association between BPA concentrations and global DNA methylation was observed in placenta samples by using targeted LINE-1 assay (Nahar et al., 2015).

DNA hydroxylmethylation is another epigenetic biomarker related to high BPA exposure. In this epigenetic modification, the C5 cytosine of the DNA is replaced with a hydroxymethyl group to form 5-hydroxymethylcytosine (5-hmc), which is considered an intermediate step in the DNA demethylation process (Richa and Sinha, 2014). Zheng et al. (2017) performed a genome-wide DNA hydroxymethylation study

using sperm samples of men who were occupationally exposed to BPA. Compared to controls without occupational BPA exposure, the total levels of 5hmc increased significantly (19.37%) in BPA occupationally-exposed men (Zheng et al., 2017). A global increase in DNA hydroxymethylation profile (72.6% of the genome) in LINE-1 repeats, imprinted genes and other important genes involved in DNA damage response was observed in BPA-exposed workers compared to non-exposed workers (60% of the genome). However, it is worth noting that this study included a relatively small sample size (30 BPA-exposed men and 26 controls) with very high urinary BPA concentrations in exposed workers (Zheng et al., 2017).

MicroRNAs (miRNAs) constitute another important epigenetic biomarker associated with BPA exposure. miRNAs are approximately 22 nucleotide long non-coding RNAs capable of regulating gene expression. Changes in the miRNA expression patterns have been observed under several disease conditions (Tüfekci et al., 2014), and also following exposure to environmental contaminants (Sollome et al., 2016). An epidemiological study performed in Italy (n = 40) observed associations between BPA concentrations in the placentas of patients undergoing therapeutic abortion and upregulation of 34 miRNAs and their target genes (De Felice et al., 2015). More specifically, a strong correlation was found between mir-146a upregulation and BPA concentrations both measured in placental tissue. In contrast, the National Children's Study (NCS) Vanguard Cohort, which involved a larger sample size (n = 110), found no association between altered miRNA levels and BPA concentrations in the placentas (Li et al., 2015). These conflicting results highlight the difficulty to interpret and identify relevant effect biomarkers specific to bisphenols exposure in human populations where exposure is complex (i.e., multiplicity of exposures, exposure misclassification issues) and biological markers not totally specific to chemical families.

The literature search has identified a wide range of epigenetic biomarkers associated with BPA exposure for different health outcomes and different biological matrices (including invasive ones such as liver samples from aborted fetuses). Notwithstanding, a prioritization is needed to ensure that some of these biomarkers can be progressively implemented in HBM studies.

3.1.1.2. Gene expression biomarkers. Gene expression profiling of mRNA transcripts in any cell type at a given time is a relevant approach to study cellular function at a global level, as well as genotype-phenotype interactions. Thus, variations in gene expression could potentially be used as relevant biomarkers of what is occurring in a given tissue, with implications for the prediction of health outcomes and elucidation of potential mechanisms (Suppl. Table 2). As a limitation, it is often unclear to which extent the assessment of gene expression in non-invasive matrices such as blood represents gene expression in a given target tissue.

Nuclear hormone receptors (NRs) constitute transcription factors that are critical for sensing the hormonal signals that regulate a wide range of physiological processes from metabolism to development (Sever and Glass, 2013). A study from Italy involving 100 male subjects reported a positive association between urinary BPA concentrations and increased expression of two estrogen-responsive genes in peripheral blood leukocytes, i.e., the estrogen receptor beta (ERβ) and the estrogen-related receptor alpha (ERRα) (Melzer et al., 2011). This study did not involve women subjects in order to avoid the bias that could possibly occur due to cyclic hormonal variations in premenopausal women. Another Italian study analyzed changes in the expression of hormone receptors in peripheral blood mononuclear cells of both fertile and infertile men from three different areas (metropolitan, urban and rural areas) (La Rocca et al., 2015). Higher concentrations of serum total BPA concentrations in infertile men were positively correlated with increased expression of nuclear receptors: ERα, ERβ, AR, AhR and PXR.

Another candidate gene associated with BPA exposure is kisspeptin (KiSS). Kisspeptins are neuroactive (hypothalamic) peptides, encoded by the KISS1 gene, that stimulate gonadotropin releasing hormone (GnRH) and play an essential role in the onset of puberty and maintenance of normal reproductive functions (Clarke et al., 2015). A study conducted on 262 mother–child pairs from China (192 pairs from an e-waste recycling town and 70 from a control area) showed that KISS1 and leptin mRNA expression levels in placental tissue were higher in the e-waste than in the control group (Xu et al., 2015). Moreover, cord blood free (unconjugated) BPA concentrations were positively associated with an increased expression of both markers (Xu et al., 2015). Due to the important role of kisspeptins in regulating puberty, they could be important effect biomarkers for assessing BPA-associated induction of precocious puberty in adolescents.

3.1.1.3. Oxidative stress and inflammatory biomarkers. Damage from endogenously produced oxygen radicals occurs to lipids in cellular membranes, proteins and nucleic acids (Halliwell and Gutteridge, 2015). Several oxidative stress biomarkers, e.g. 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-OHdG or 8-oxodGuo), malondialdehyde (MDA) and 8-*iso*-prostaglandin $F_{2\alpha}$ (8-isoprostane), have been studied for decades and are included in several AOPs (e.g. 8-OHdG in AOP 17 and MDA in AOP 260) (Hofer, 2001). However, their use in environmental epidemiological studies investigating health effects related to non-persistent chemical's exposure is recent.

Several oxidative stress biomarkers were identified in 14 epidemiological studies assessing bisphenols (Suppl. Table 3). Overall, the studies indicated that exposure to BPA mainly assessed in urine was positively associated with increased urinary levels of 8-OHdG, MDA and/or 8-isoprostane to some extent (Asimakopoulos et al., 2016; Kim and Hong, 2017; Lv et al., 2016; Watkins et al., 2015; Yang et al., 2014a; Yang et al., 2009; Yi et al., 2011; Zhang et al., 2016). On the contrary, a few studies found no associations (Erden et al., 2014b; Hong et al., 2009), while results were inconsistent in others (for instance, Huang et al. (2017) found a positive association with 8-isoprostane, but not with 8-OHdG). No studies reported negative associations for any of the oxidative stress biomarkers evaluated and BPA exposure. Two studies reported positive associations between exposure to the structural analogue BPS and higher urinary 8-OHdG levels (Asimakopoulos et al., 2016; Zhang et al., 2016). There are methodological issues of concern related to artefactual MDA formation and lack of HPLC separation in some studies (Grotto et al., 2009), and therefore 8-OHdG and 8-isoprostane excreted and measured in urine appear as the most suitable markers of oxidative stress related to bisphenols exposure.

The mechanisms by which BPA induces oxidative stress are not completely elucidated (Gassman, 2017). The main metabolic pathway for bisphenols is by conjugation leading to glucuronide or sulfate conjugates that are mainly excreted in urine. A minor metabolic pathway described is cytochrome *P*-450-mediated hydroxylation to a catechol, followed by further transformation to an *o*-quinone (Kovacic, 2010), being the latter capable of redox cycling with generation of ROS (Kovacic, 2010; Sakuma et al., 2010).

Other oxidative stress markers measured included o,o'-di-tyrosine (formed from oxidation of two nearby tyrosines within proteins that underwent hydrolysis); 3-chloro-tyrosine (from neutrophil myeloperoxidase release of hypochlorous acid (HOCl) reacting with tyrosine); markers of nitrosative stress (e.g. 8-nitro-guanine and 3-nitro-tyrosine) formed from reaction with the oxidants peroxynitrite anion ($ONOO^-$) or nitrogen dioxide (NO_2), but also total thiols and GSH levels (sulfhydryl -SH groups are susceptible to oxidative damage, which can lower the SH concentration). Additionally, assessment of protein carbonyls (adducts to protein formed from metal-catalyzed oxidation of amino acids or from aldehyde including lipid peroxidation reactions) and activities or genetic polymorphisms (e.g. antioxidant enzymes such as catalase and glutathione peroxidase) were also reported. Although less studied in relation to bisphenols, urinary HNE-MA (4-hydroxy-2-nonenal-mercapturic acid) has potential for becoming a reliable biomarker of lipid

Table 2
Inventory of bisphenol-related hormonal, metabolic and allergy/immune effect biomarkers in HBM studies.

Biomarkers	Matrix	Health Endpoint	Number of studies	Strengths	Limitations	Conclusions
				Reproductive Biomarkers		
TT, E2, LH, FSH, SHBG Additional estimations: fT, FAI, TT/E_2, FAI/LH, FSH/LH	Serum	HPG axis / Reproduction /Behavior /Metabolism disorders	29 (Table S4)	Strong support from experimental studies. Hormonal concentrations can be compared to population reference values. Relationships and ratio among related hormones can provide information on enzymatic activity and also provides information on feedback loops.	Diurnal and seasonal variations. Requires the consideration of sex and developmental periods (e.g., males vs. females, children vs. adolescents/adults, phase of the menstrual period). A limited number of studies assessed the five components of this set of biomarkers. Not specific to bisphenols or to specific chemical families.	Requires a more comprehensive characterization of the hormonal axis, standardized collection of sample and measurements with quality controls. Careful consideration of timing of developmental period and sex regarding timing of sampling and set of effect biomarkers to assess. This initial set of reproductive hormones must be coupled to other more specific biomarkers of a given tissue, to gain precision.
INSL3/ INHB/ AMH	Serum	Testicular function and descent	1 (INSL3) 8 (INHB) (Table S4)	INSL3 regulates testicular descent and is constitutively expressed in Leydig cells.AMH is a marker of Sertoli cells maturation. INHB reflects Sertoli function and the status of the testis germinative epithelium. Additionally, it regulates FSH secretion from the pituitary.	Although not specific for particular chemical families, it can be more specific for those chemicals targeting male reproductive organs. AMH has not been previously studied in relation to BPA exposure.	When combined with other HPG hormones and semen parameters, these biomarkers can help to gain precision regarding the male reproductive system. Although less explored, some of these markers can also provide information on female reproductive tissues.
DHT/ PREG/17-OHPREG/ DHEA-S/ PRL/ P4/ E_1/ E_3	Serum	Steroidogenesis	11(Table S4)	The assessment of other steroids can help to detect potential disruptions of the steroidogenesis process beyond the more classic reproductive hormones normally studied.	Because not all steroids can be evaluated, the prioritization of additional steroidogenic markers should be substantiated on mechanistic and/or AOP knowledge.	Some of these steroids can provide extra information on specific pathways based on experimental hypotheses.
E1, E_2, and hydroxilated metabolites: 2-OH-E_1, 2-OH-E_2, 4-OH-E_1, 4-OH-E_2	Urine	Estrogenic metabolism /Breast cancer	2 (Table S4)	Assessing urinary concentrations of hydroxy-estrogens provides information on estrogen metabolism and excretion pathways, which may be a predictor of oxidative stress, endocrine alterations and even of the risk of developing breast cancer risk in women.	Effect biomarkers measured in urine should always be corrected for urinary dilution. Any alteration in renal function could bias both exposure and effect biomarker measurements.	As urine constitutes the most accessible matrix in HBM studies, research and validation of effect markers measured in urine is important. An altered estrogen metabolism can be an important factor resulting in negative effects of prolonged exposure to BPA.
KiSS	Serum	Ovulation Pregnancy Puberty Onset	1 (Table S4)	BPA actions on Kisspeptinergic neural systems are experimentally supported. Kisspeptinergic neurons integrate reproductive and metabolic inputs at a central level, to then coordinate downstream signaling involving GnRH release at hypothalamus, and consequently LH and FSH levels at the pituitary.	Limited data on variability of human serum KiSS levels and reference values are not available. The role of KiSS on human physiology is not fully understood. Not specific to chemical families, but more specific to those chemicals such as bisphenols, known to exert effects in the hypothalamus.	KiSS plays an important role on ovulatory control in adult females, pregnancy, and it is crucial for puberty onset. KiSS levels should be combined with other biomarkers of the HPG axis. A cross-talk exists between kisspeptinergic neurons and leptin, that may explain KiSS role on metabolic health and vice versa. This novel effect biomarker should be further explored at different biological levels (DNA, RNA, protein…) in HBM studies.
sFlt1:PlGF	Serum	Placental function / Pregnancy outcomes	1(Table S4)	The sFlt1:PlGF ratio may predict pregnancy complications such as preeclampsia and fetal growth restriction.	Not specific for a given chemical. Absence of population reference values.	The sFlt1:PlGF ratio is a promising and understudied marker of placental function that could help to understand mechanisms of placenta-related adverse effects in relation to BP exposure and other environmental chemicals during pregnancy.
Semen quality parameters	Semen samples	Spermatogenesis / Fertility	7 (Table S5)	Human sperm parameters such as sperm count, concentration, morphology and vitality, present the advantage of examining a localized tissue in a non-invasive way. Additionally, seminal plasma offers the possibility of measuring exposure biomarkers and hormonal parameters in the same matrix.	While sperm collection in adult men is feasible, obtention of samples during puberty and adolescence (one of the most critical periods for spermatogenesis) is more complex. Not specific for a chemical family, but more specific to those chemicals known to impact spermatogenesis.	Semen constitutes a non-invasive sample that can provide both *in situ* exposure and effect data, specific to the male reproductive system, and at different levels of organization: from cell counts and functional aspects, to seminal hormones, and sperm epigenetic and gene expression markers. Future studies should take advantage of integrating these possibilities.

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Table 2 (*continued*)

Biomarkers	Matrix	Health Endpoint	Number of studies	Strengths	Limitations	Conclusions
				Glucocorticoid biomarkers		
Cortisol	Serum and saliva	HPA axis / Stress Response	3 (Table S6)	Emerging evidence suggest that BPA may disrupt the hypothalamic–pituitaryadrenal (HPA) axis altering the stress response in experimental animals. Cortisol plays a crucial role in the stress response, as well as metabolic health. There exist population reference levels.	Not specific for a given chemical.Subjected to daily variations. While repeated blood sampling is more complicated, especially in children, repeated cortisol measurements in saliva is feasible.	Although only 3 epidemiologic studies have studied cortisol in response to BPA exposure, these preliminary results call for further research. A more complete characterization of the HPA axis would be desirable, including the measurement of serum CRH and ACTH levels apart from cortisol.
				Thyroid biomarkers		
TSH, FT_3, FT_4, TT_3, TT_4	Serum	HPT axis /Neurodevelopment and Metabolism	11(Table S7)	Thyroid hormones are considered upstream biomarkers of neurodevelopment and metabolic health. Even subclinical dysfunction of thyroid homeostasis during pregnancy may affect offspring neurodevelopment. TSH levels are readily available from neonatal blood tests in most industrialized countries.	Not specific for a given chemical. TSH secretions exhibit circadian rhythms which can mask subtle variations. Circulating TH levels are less affected, due to the existence of an extrathyroidal pool. Not all studies have measured this same set of thyroid biomarkers, hindering interpretations especially in the case of discordant results.	Additional research using more complete datasets pertaining to the HPT axis are needed. Repeated measures throughout time are advisable. Iodine intake should be considered. No previous studies have considered the gene expression or DNA methylation of thyroid receptors in PBMCsin relation to bisphenols exposure.
TPOab	Serum	Antithyroid autoantibodies (Immune System-Thyroid disruption)	6 (Table S7)	Autoimmune thyroid disease causes cellular damage and alters thyroid gland function when sensitized T-lymphocytes and/or autoantibodies bind to thyroid cell membranes, causing cell lysis and inflammatory reactions. The presence of thyroperoxidase (TPO) autoantibodies is an early predictor of thyroid dysfunction.	Not specific for a given chemical. There exist other thyroid related autoantibodies, including the antithyroglobulin antibody (TgAb) and the TSH receptor antibody (TRAb).	The assessment of thyroid autoimmunity provides a more exhaustive characterization of thyroid disruption. TPOab was positively associated with higher serum BPA concentrations in adults, although not in all studies. Future studies should incorporate TPOab in conjunction with classic thyroid hormones to better identify susceptible euthyroid subjects before development of thyroid disease.
				Metabolic biomarkers		
Glucose and Insulin / HOMA HbA1c	Serum	Glucose homeostasis	18 (Glucose and/or insulin) 10 (HOMA) 4 (HbA1c)(Table S8)	The relationship between fasting glucose and insulin levels calculated through the HOMA index, constitutes a validated biomarker of β-cell function and insulin resistance. There is strong experimental support for low-dose BPA actions on glucose homeostasis. HbA1c provides information on dysregulated glucose levels during the previous months.	Not specific. Differences between children and adult populations should be considered.	The HOMA index is a validated biomarker of interest for glucose homeostasis to detect both subclinical and clinical effects (e.g., classifying prediabetic and type 2 diabetes subjects). HbA1c complements HOMA data with the cumulative glycemic history. Future studies should test whether exposure to bisphenol analogues are associated with an altered glucose homeostasis.
TG, TC, HDL-C, LDL-C	Serum	Lipid metabolism	6 (Table S8)	Serum lipids have been traditionally used in relation to cardiometabolic health. There are reference and cut-off values for these biomarkers.	Not specific. Although these markers could be useful in adult and elder populations, they may not be enough sensitive for children, given the lack of associations reported, with the exception of obese children.	Although serum lipids are important diagnostic components of the metabolic syndrome, its utility in relation to bisphenols exposure is not clear, particularly in children populations.Other metabolic markers different from serum lipids may be more sensitive to bisphenols exposure.
Leptin/ Adiponectin among other adipokines	Serum	Adipose tissue function	6 (Table S8)	Leptin secretion by adipose tissue is proportional to fat mass and regulates energy balance. While leptin upregulates proinflammatory cytokines related to insulin resistance, adiponectin exerts opposing anti-inflammatory and insulin-sensitizing actions.	Not specific. There exists less studied adipokines such as ghrelin, visfatin, omentin, resistin, etc.	The leptin/adiponectin ratio is regarded as a marker of adipose tissue (dys)function, related to insulin sensitivity. Adipokine levels seem to be sensitive markers of BPA-related metabolic disruption in both children and adults. The combined measurement of adipokines levels with glucose homeostasis is especially encouraged in future studies assessing exposure to both BPA and its analogues.

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Table 2 (*continued*)

Biomarkers	Matrix	Health Endpoint	Number of studies	Strengths	Limitations	Conclusions
ALT, AST, GGT, ALP, LD	Serum	Liver function	4 (Table S8)	Reference levels for these classic liver markers exist. ALT is primarily localized in the liver, while AST is present in several tissues. Their ratio helps to identify the etiology of liver damage (e.g., viral, alcohol, steatosis…). LD and ALP are less specific to the liver since they are also present in other tissues. For example, elevated ALP levels can indicate both liver or bone damage. However, if both ALP and GGT levels are increased, will be indicative of a cholestatic disorder.	Not specific. These markers are not always specific for the liver, and other tissues can contribute to altered levels. Liver markers may not be sensitive enough to map subclinical effects of exposure to environmental chemicals in healthy populations. In contrast, they may be interesting for susceptible populations including obese children and adults, elders, subjects with medication affecting liver dynamics or alcohol consumption.	Liver biomarkers can be combined to inform about different forms of liver damage: steatosis, obstruction, fibrosis and/or necrosis. Future studies should confirm or rule out the relationship between liver function biomarkers and bisphenols exposure, especially in susceptible populations.
ACR	Urine	Endothelial function	3 (Table S8)	The ACR is a biomarker of early endothelial dysfunction in both children and adults. Its measurement in urine means that it can be implemented in pediatric populations without the need of sampling blood.	Not specific. ACR is not specific to a given organ, but provides information on the renal and endothelial system function.	Apart from BPA, preliminary data has shown that BPS exposure is also associated with higher ACR levels in children. Therefore, the ACR should be further studied as a potential marker endothelial dysfunction in relation to bisphenol exposure.
CRP/ hs-CRP	Serum	Systemic Inflammation	3 (Table S8) 4 (Table S3) 1 (Table S9)	C-reactive protein (CRP) is an acute phase protein produced by the liver in response to inflammation. It is an important predictor of cardiometabolic and other chronic diseases.	Not specific of chemicals or tissue localization. CRP is neither specific to a given organ or disease. Although hs-CRP is preferred over standard CRP measurements, only one of the studies assessing CRP measured this form.	CRP should be combined with markers more specific of metabolic health (e.g., glycemic biomarkers, adipokines, hepatic markers…). Although CRP is a non-specific marker of systemic inflammation, it may capture disruptions at different levels of biological organization. Thus, CRP may be an interesting biomarker for assessing mediation effects in epidemiologic studies assessing exposure-metabolic disease associations.
IL-6, IL-10,TNF-α	Serum	Interleukins / Inflammation	2 (Table S8) 2 (Table S3) 1 (Table S9)	Inflammatory cytokines are signaling molecules predominantly produced by T immune cells and macrophages, as well as cells regulating inflammatory processes. Thus, they may provide additional information on the tissues or pathways affected.	Not specific of chemicals or tissue localization.	Investigating the serum profile of pro- and anti-inflammatory cytokines may help elucidate pathways activated by bisphenols and other environmental chemicals. Ideally, they should be coupled to other more specific metabolic markers in order to gain precision and facilitate data interpretation in human studies.
Vitamin D	Serum	Metabolic function	3 (Table S8)	Vitamin D receptors have been found in many tissues, including the cardiovascular, immune and reproductive systems.	Not specific. Not specific for a specific organ. More mechanistic studies are needed.	Further studies are warranted to understand the possible interaction between bisphenols and altered levels of the so-called "hormone D" in relation to both reproductive and metabolic adverse effects.
				Allergy/Immune markers		
IgE	Serum	Antibodies / Food and contact allergies	3 (Table S9)	IgE and specific IgE antibodies play an important role in allergic (atopic) processes including asthma.	Not specific. The predictive potential of total IgE differs according to asthma and allergy subtypes.	IgE has been shown to partially mediate the effect of prenatal BPA exposure on the risk of asthma development in children. This potential mediating role of total IgE and specific IgE antibodies in BPA-related allergic sensitization should be further explored.

Abbreviations: ACR (albumin-creatinine ratio); ALP (alkaline phosphatase); AMH (anti-müllerian hormone); ALT (alanine aminotransferase), AST (aspartate aminotransferase); CRP (c-reactive protein); DHEA-S (dehydroepiandrosterone sulfate); DHT (dihydrotestosterone); E1 (estrone); E2 (17-β-estradiol); E3 (estriol); FAI (free androgen index); FSH (follicular stimulating hormone); fT (free Testosterone); FT3 (free triiodothyronine); FT4 (free thyroxine); GGT (gamma-glutamyl transaminase); HbA1c (glycated hemoglobin); HDL-C (high-density lipoprotein cholesterol); HOMA (homeostasis model assessment); HPG (hypothalamus-pituitary–gonadal); hs-CRP (high-sensitivity c-reactive protein); IgE (immunoglobulin E); IL (interleukin); INHB (Inhibin); INSL3 (insulin-like peptide 3); KiSS (kisspeptin); LD (lactate dehydrogenase); LDL-C (low-density lipoprotein cholesterol); LH (luteinizing hormone); PREG (pregnenolone); PRL (prolactin); P4 (progesterone); sFlt1:PlGF (soluble fms-like tyrosine kinase 1 to placental growth factor ratio); SHBG (sex hormone-binding globulin); TC (total cholesterol); TG (triglycerides); TNF-α (tumor necrosis factor alpha); TPOab (thyroperoxidase antibodies); TSH (thyroid stimulating hormone); TT (total testosterone); TT3 (total triiodothyronine); TT4 (total thyroxine); 2-OH-E1 (2-hydroxy-estrone); 2-OH-E2 (2-hydroxy-17β-estradiol); 4-OH-E1 (4-hydroxy-estrone); 4-OH-E2 (4-hydroxy-17β-estradiol); 17OHPREG (17α-hydroxypregnenolone).

peroxidation, which was recently associated with both higher urinary BPA and BPF concentrations (Wang et al., 2019).

Oxidative stress biomarkers comprehensively capture disruptions at various levels of biological organization. As a limitation, these biomarkers are not specific for a given exposure such as BPA, or for a unique organ or system, and can also originate from external sources such as food.

3.1.2. Biochemical effect biomarkers

Biochemical effect biomarkers identified in the literature search are summarized in Table 2.

3.1.2.1. Reproductive hormones (RHs). RHs coordinate a myriad of physiological functions. The most important ones include their role in sexual differentiation of both gonads and brain during development, but also on metabolic organs (Bao and Swaab, 2011). Additionally, RHs maintain these functions during adulthood. In total, 32 studies reporting biomarker data on reproductive hormones were retrieved from the literature search and organized based on similar windows of development and/or study designs (Suppl. Table 4). The most relevant articles are discussed below.

Few studies explored associations between prenatal BPA exposure and maternal or offspring sex hormone levels. Prenatal urinary BPA concentrations were associated with decreased total testosterone (TT) cord blood levels and testosterone:17β-estradiol (T/E2) ratio among male neonates (Liu et al., 2016); whereas cord blood BPA concentrations were associated with lower cord blood insulin-like peptide 3 (INSL3) levels but not with TT in a case-control study of cryptorchidism (Chevalier et al., 2015). INSL3 is a major regulator of testicular descent, and a marker of Leydig cells maturation. Since INSL3 is not acutely regulated by the hypothalamus-pituitary (HP) axis, but is constitutively secreted by Leydig cells, it is considered a valid marker for their number and status (Sansone et al., 2019) that could be further implemented in environmental epidemiologic studies, together with anti-Müllerian hormone (AMH), an analogous marker of Sertoli cells maturation (Sansone et al., 2019).

Peripuberty and adolescence represent understudied critical periods which can also be affected by environmental chemical exposures. Urinary BPA concentrations during the second trimester of gestation were associated with higher serum inhibin B (INHB) levels in peripubertal boys, and with higher TT levels in peripubertal girls (Watkins et al., 2017a, 2017b). INHB is produced by Sertoli cells, and its levels directly reflect the status of the testis germinative epithelium. Low INHB levels have been associated with low testicular function and/or with alterations of testicular parameters at histological examination (Esposito et al., 2018). Urinary BPA concentrations were cross-sectionally associated with increased serum TT levels and reduced cortisol in prepubertal 9–11 year-old boys (Mustieles et al., 2018b). Additionally, urinary BPA concentrations were negatively associated with serum TT levels among male adolescents and positively associated with TT levels in female adolescents in the 2011–2012 National Health and Nutrition Examination Survey (NHANES) (Scinicariello and Buser, 2016). As previously observed in animal studies, there exists a complex relationship between BPA and reproductive hormones, which greatly depends on the dose, sex and timing at which exposure occurs (discussed in detail in Mustieles et al. 2018b).

A case-control study on precocious puberty in girls found that higher urinary BPA concentrations correlated with higher urinary concentrations of TT, E2 and pregnenolone (PREG) (Lee et al., 2014b), while a very small study comparing 28 cases of precocious puberty in girls with 28 controls did not find associations between urinary BPA and serum E2 or KiSS levels (Özgen et al., 2016). However, KiSS levels significantly differed among cases and controls (Özgen et al., 2016). KiSS controls the hypothalamic secretion of GnRH and is consequently implicated in puberty onset, fertility and pregnancy outcomes (Skorupskaite et al., 2014). Given that KiSS appears to be a target of BPA exposure in both rodents and non-human primates (Kurian et al., 2015; Patisaul, 2013), it should be further investigated in HBM studies.

BPA has been proposed as a risk factor for PCOS, and three case-control studies were retrieved from the search. Serum BPA concentrations were associated with increased serum TT and androstenedione (AD) levels in adult women (Kandaraki et al., 2011) and with higher TT, free testosterone (FT) and dehydroepiandrosterone sulfate (DHEA-S) levels among adolescents (Akın et al., 2015). Additionally, another case-control study in women with PCOS found a positive association between serum BPA concentrations and the free androgen index (FAI) (Tarantino et al., 2013). These initial results suggest that BPA-related ovarian toxicity may be stronger in PCOS patients. Given the increasing prevalence of this condition, further research is warranted.

BPA may impact female fertility through actions in both the ovary and the HP axis, converging in abnormal estrous cyclicity (Viguié et al., 2018). One of the main molecular targets inside the ovary would be aromatase inhibition in antral follicles, through which the production of E2 from T would decrease (Viguié et al., 2018). Mok-Lin et al. (2010) studied 84 women undergoing fertility treatment finding that higher BPA concentrations measured in two urine samples were associated with reduced E2 peak levels and reduced oocyte count. These results were confirmed in a follow-up study including 174 women by Ehrlich et al. (2012). However, the latest follow-up of this study with 256 women did not replicate previous findings (Mínguez-Alarcón et al., 2015), which may be influenced by the progressive decline in BPA concentrations observed over the years in the U.S. (LaKind et al., 2019). Bloom et al. (2011) studied 44 women attending another fertility clinic and also found that free serum BPA concentrations were inversely associated with E2 levels, but this time no association was observed between BPA concentrations and oocyte count. Finally, a study including 106 occupationally exposed and 250 non-occupationally exposed women reported increased serum prolactin (PRL) and progesterone (P4) levels among all females in response to higher urinary BPA concentrations. However, when only occupationally exposed participants were considered, higher BPA exposure was additionally associated with increased serum E2, while reduced follicle stimulating hormone (FSH) levels were only observed in non-occupationally exposed women (Miao et al., 2015). The results from Miao et al. (2015) suggest that different biomarker profiles may be observed in response to different BPA concentrations and/or exposure routes (Miao et al., 2015). In other occupational studies, in which inhalation and dermal absorption are thought to be the main exposure routes leading to high internal levels of free BPA (Hines et al., 2018), different effects would also be expected compared to the general population.

Although the study of reproductive biomarkers in women is particularly complex due to hormonal variations during different phases of the menstrual cycle, the still limited but suggestive evidence calls attention for further HBM studies to correctly address this hypothesis strongly substantiated by toxicological data (Peretz et al., 2014; Viguié et al., 2018).

Out of the 10 studies retrieved on BPA and reproductive hormones in adult men, all found significant associations with at least one reproductive hormone; however, not all of them were conducted under the same setting and neither reported consistent relationships (Suppl. Table 4). In men recruited from the general population, Galloway et al. (2010) observed that BPA concentrations measured in one 24-hour urine sample were associated with higher serum TT levels, in line with Lassen et al. (2014) who reported associations between urinary BPA concentrations and increased serum TT, FT, E2, and luteinizing hormone (LH) levels. In contrast, Mendiola et al. (2010) reported that urinary BPA was negatively associated with FAI and the FAI/LH ratio, and positively associated with serum sex hormone-binding globulin (SHBG) levels. In men attending a fertility clinic, urinary BPA concentrations were negatively associated with serum INHB levels and the E2:TT ratio, and positively associated with FSH and the FSH:INHB ratio (Meeker et al., 2010a). Den Hond et al. (2015) observed reduced serum

TT levels in response to higher urinary BPA concentrations from males seeking fertility care. Vitku et al. (2016) assessed BPA concentrations and 11 steroid hormones in the plasma and seminal plasma of male attending a fertility center. Plasma BPA was positively correlated with estrone (E1), E2, PREG, 17-OH-PREG and DHEA, while negatively associated with dihydrotestosterone (DHT) levels. In contrast, seminal BPA was negatively associated with P4, 17-OH-P4 and DHEA, but similarly correlated with E2 and estriol (E3) (Vitku et al., 2016). Among the strengths of Vitku et al. (2016) are the measurement of both BPA exposure and hormone biomarkers using a previously validated hyphenated mass spectrometry methodology in circulating blood and semen. In studies with occupationally and non-occupationally exposed men, higher serum BPA concentrations were associated with reduced serum AD, FT and FAI, and increased SHBG levels (Zhou et al., 2013), as well as with reduced serum AD and increased SHBG levels (Zhuang et al., 2015). Additionally, urinary BPA was associated with increased levels of PRL, E2 and SHBG, as well as with reduced serum levels of FSH, AD and FAI (Liu et al., 2015).

BPA exposure has also been related to lower sperm counts and/or poorer semen quality (Suppl. Table 5). In several cross-sectional studies, urinary BPA concentrations were associated with poorer semen parameters in adults (Knez et al., 2014; Lassen et al., 2014; Li et al., 2011; Meeker et al., 2010b), while in others were not (Goldstone et al., 2015; Mendiola et al., 2010). Interestingly, Vitku et al. (2016) found that BPA concentrations assessed in seminal plasma, but not in blood plasma, were negatively correlated with sperm count, concentration and morphology, suggesting that circulating BPA concentrations may not have the same biological meaning than exposure measured at this localized fluid. Semen is produced by different organs and constitutes a non-invasive biological sample that fits very well the exposure-effect biomarker paradigm discussed in this work, since it can provide *in situ* exposure and effect data specific to the male reproductive system, and at different levels of biological organization: from cell counts and sperm morphology/vitality, to seminal hormones, and sperm epigenetic and gene expression markers (Bonache et al., 2012), among many other molecular markers (Sutovsky and Lovercamp, 2010) and omics approaches (Huang et al., 2019).

Among Korean male and female adults participating in a large national biomonitoring survey, urinary concentrations of E1, E2 and their hydroxylated metabolites were higher in the participants with highest urinary BPA concentrations compared to the low-exposed group. Estrogen metabolism to 4-hydroxy-E1 and 4-hydroxy-E2 was more active than that to 2-hydroxy-E1 and 2-hydroxy-E2 among participants in the high BPA exposure group, with possible implications for breast cancer and other endocrine disorders (Kim et al., 2014).

BPA has previously been associated with neonatal outcomes including lower birth weight and preterm birth in epidemiologic studies (Mustieles et al., 2020, 2018c; Pergialiotis et al., 2018), although underlying mechanisms are poorly understood. Ferguson et al. (2015) found that maternal urinary BPA concentrations measured at four times during pregnancy were associated with higher plasma levels of soluble fms-like tyrosine kinase-1 (sFlt-1), and a higher sFlt-1/placental growth factor (PlGF) ratio, suggesting a disrupted placental development. Among the strengths of Ferguson et al., (2015) are the repeated collection and measurement of BPA in urine and of sFlt-1/PlGF in serum up to four times throughout pregnancy using validated methodologies. While PlGF is a pro-angiogenic placental protein, which plays an important role in vascularization, sFlt-1 binds to PlGF making it anti-angiogenic. Lower circulating levels of PlGF and higher levels of sFlt-1 during pregnancy predict pregnancy complications such as pre-eclampsia and fetal growth restriction (Ferguson et al., 2015). The sFlt-1:PlGF ratio is a promising effect biomarker of placental function that should be further explored.

Overall, the results show that serum LH, FSH, E2, TT and SHBG levels are the reproductive markers more frequently evaluated in HBM studies in both children and adult populations (Table 2). The measurement of SHBG levels allows the estimation of FT levels and FAI (Table 2). The E2:TT ratio is used as a measure of aromatase activity. TT:LH and FSH:INHB ratios are employed as biomarkers of Leydig and Sertoli function, respectively (Meeker et al., 2010a). Other useful and less studied effect biomarkers are INHB and AMH levels as markers of Sertoli function, and INSL3 as a marker of Leydig function (Table 2). Additionally, the adrenal androgen DHEA-S and cortisol have been studied as biomarkers of adrenarche in prepubertal children, and KiSS as biomarker of puberty onset. The sFlt1:PlGF ratio should also be further explored as a marker of placental function. Other less studied markers include AD, DHT, PRL, PREG and P4 (Table 2). One of the main shortcomings observed across studies is the absence of a harmonized panel of hormonal markers to assess a specific function in a particular age group. Importantly, several hormonal biomarkers should be assessed in combination to adequately characterize a complete biological pathway. This approach may counteract the variability associated with steroid hormone levels and account for feedback regulations, facilitating data interpretation.

3.1.2.2. Glucocorticoid hormones. Increasing evidence shows that BPA, among other environmental chemicals, may disrupt the hypothalamic–pituitaryadrenal (HPA) axis altering the stress response (Michael Caudle, 2016). However, scarce human data is available (Suppl. Table 6). In a longitudinal birth cohort, higher maternal urinary BPA concentrations at second trimester of pregnancy were associated with a dysregulation of the maternal daytime cortisol pattern in saliva, including reduced cortisol at waking and a flatter daytime pattern (Giesbrecht et al., 2016). In a consecutive study, the offspring of these women was followed-up and cortisol levels were measured in infant's saliva before and after an infant stressor (blood draw) at 3 months of age (Giesbrecht et al., 2017). The authors found that maternal prenatal urinary BPA concentrations were associated with increases in baseline cortisol levels among female infants but decreases among males (Giesbrecht et al., 2017). In contrast, after the blood draw (i.e. the stressor), maternal BPA concentrations were associated with increased cortisol compared to baseline levels among males, but decreased levels among female infants, suggesting a sex-specific effect of BPA on HPA-axis function (Giesbrecht et al., 2017). In peripubertal boys from the Spanish INMA-Granada cohort, higher urinary BPA concentrations were cross-sectionally associated with reduced serum cortisol levels and a higher TT:cortisol ratio, suggesting a potential effect at the adrenal gland (Mustieles et al., 2018b). More studies are needed to further elucidate the role of BPA exposure on the stress response, preferably with a more complete characterization of the HPA axis (Table 2).

3.1.2.3. Thyroid hormones (THs). THs play critical roles in differentiation, growth, and metabolism and are required for the normal function of all tissues (Yen et al., 2006), most notably for normal brain development (Bernal, 2005). While various MoAs underlying BPA's effect on the hypothalamic-pituitary-thyroid (HPT) axis are described in experimental studies (Dang et al., 2009; Moriyama et al., 2002; Sheng et al., 2012), epidemiologic studies are scarce and the majority differ in scope, focus and consequently in the effect biomarkers tested (Table 2 and Suppl. Table 7). Overall, associations between BPA exposure and circulating THs are difficult to interpret in the cases when significant associations are described, calling for additional research using more complete datasets pertaining to the HPT axis. Nonetheless, while not consistently significant, an inverse association between BPA and thyroid-stimulating hormone (TSH) is repeatedly observed in adults (Meeker et al., 2010a) in conjunction with increased free triiodothyronine (FT3) (Wang et al., 2013) or decreased total thyroxine (TT4) (Meeker and Ferguson, 2011) in pregnant women (Aung et al., 2017) and in newborns (Brucker-Davis et al., 2011; Chevrier et al., 2013; Romano et al., 2015). Additionally, free thyroxine (FT4) and serum BPA levels were negatively correlated

in men (Sriphrapradang et al., 2013) and positively correlated in pregnant women (Aker et al., 2016; Aung et al., 2018). Assessment of thyroid autoimmunity provides a more exhaustive characterization of thyroid disruption. In the only study focused on thyroid autoimmunity, thyroid peroxidase autoantibodies (TPOab) positivity was significantly higher across increasing serum BPA quartiles in adults (Chailurkit et al., 2016).

Birth cohorts have also reported an inverse relationship between maternal BPA exposure and maternal TSH (Aung et al., 2017) and sex-specific TSH levels in newborns (Chevrier et al., 2013; Romano et al., 2015). Since mild or transient variations in THs during development affect offspring cognitive outcomes (Bernal, 2005), further investigation is warranted.

3.1.2.4. Metabolic biomarkers. BPA is a suspected obesogenic compound that promotes fat accumulation in experimental animals (Wassenaar et al., 2017), but also a metabolic disruptor able to alter glucose homeostasis at very low doses (Alonso-Magdalena et al., 2015), and to alter satiety signals (Heindel et al., 2017). Below we summarize and discuss the most important biomarkers of whole-body metabolism retrieved (Table 2 and Suppl. Table 8).

Few studies have explored the association between BPA exposure during pregnancy and maternal glucose homeostasis. Urinary BPA concentrations at second trimester, but not first trimester of pregnancy, were positively associated with blood glucose levels 1-hour after a 50-g glucose challenge test at 24–28 weeks of gestation (Chiu et al., 2017). However, a case-control pilot study and a prospective mother–child cohort study that evaluated urinary BPA during the first trimester did not find a higher risk of gestational diabetes mellitus (Robledo et al., 2013; Shapiro et al., 2015).

The HOMA-IR is a validated biomarker based on fasting glucose and insulin levels used to quantify peripheral insulin resistance and pancreatic beta-cell function (HOMA-B) (Borai et al., 2011). In children, some studies have found higher HOMA-IR values in response to higher BPA concentrations, especially among obese subjects (Khalil et al., 2014; Lee et al., 2013; Menale et al., 2017), while others have not (Eng et al., 2013; Watkins et al., 2016). Adipokine levels seem to be early metabolic indicators of BPA exposure. Leptin secretion by adipose tissue is proportional to fat mass and regulates energy balance. While leptin upregulates proinflammatory cytokines related to insulin resistance, adiponectin exerts opposing anti-inflammatory and insulin-sensitizing actions (López-Jaramillo et al., 2014). Several studies in neonates (Ashley-Martin et al., 2014; Chou et al., 2011), children (Menale et al., 2017; Volberg et al., 2013; Watkins et al., 2016) and adults (Rönn et al., 2014; Zhao et al., 2012) suggest that both leptin and adiponectin (and probably other adipokines) could be sensitive early markers of BPA metabolic disruption, especially important in the case of infants and children. Although the previous studies varied in study design, critical window of development and matrix for BPA exposure assessment, they point to a similar direction. Importantly, Menale et al. (2017) confirmed their observational findings in adipocytes isolated from eight prepubertal children, showing a decrease in adiponectin after *in vitro* BPA dosing. This is in line with described BPA actions in the adipose tissue of experimental animals (Wassenaar et al., 2017), as well as previously reported associations between BPA exposure and obesity in children (Kim et al., 2019; Mustieles et al., 2019) and possibly in adults (Oppeneer and Robien, 2015; Rancière et al., 2015). Therefore, the use of these markers of adipose tissue function should be encouraged. On the contrary, serum lipids [triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C)] do not seem to be sensitive biomarkers of BPA-related metabolic effects in children (Eng et al., 2013; Khalil et al., 2014; Perng et al., 2017).

The relationship between adult BPA exposure and biomarkers of glucose homeostasis has been relatively well-studied, mostly under a cross-sectional design. Higher BPA concentrations have been associated with increased glycated hemoglobin (HbA1c) levels in adults from the NHANES (Silver et al., 2011) and adult men from the Canadian Measures Health Survey (CMHS) (Tai and Chen, 2016). In the NHANES, urinary BPA was positively associated with greater serum insulin levels and insulin resistance (HOMA-IR) (Beydoun et al., 2014), higher risk of prediabetes (Sabanayagam et al., 2013), and higher chances of type 2 diabetes mellitus (T2DM) independently of other risk factors (Shankar and Teppala, 2011). Other Asiatic cross-sectional surveys have also reported similar results for the risk of T2DM (Aekplakorn et al., 2015; Ning et al., 2011), and insulin resistance (Wang et al., 2012). Moreover, a prospective study identified a susceptible group of adults for BPA effects on glucose homeostasis based on a genetic risk score (Bi et al., 2016). Fasting circulating glucose and insulin levels, together with HOMA (-IR and -B) estimations constitute valid biomarkers of insulin resistance, prediabetes and T2DM, which have been consistently associated with BPA exposure (Hwang et al., 2018). Future studies should evaluate whether BPA substitutes can also interfere with glucose homeostasis.

Similar to studies in children, serum lipid levels in adults do not seem to be good metabolic biomarkers for BPA effects (Lang et al., 2008; Milošević et al., 2017; Savastano et al., 2015). In contrast, several associations have been reported for liver enzymes, including clinically abnormal serum levels of gamma glutamyl transpeptidase (GGT), lactate dehydrogenase (LD) and alkaline phosphatase (AP) in adults from the NHANES (Lang et al., 2008; Melzer et al., 2010), and increased serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and GGT levels in elderly (Lee et al., 2014a). More studies are needed to elucidate whether BPA exposure could impact liver function in adults.

Low-grade chronic inflammation is closely related to obesity and metabolic syndrome (Saltiel and Olefsky, 2017). BPA exposure has been associated with higher levels of serum inflammatory markers such as interleukin (IL)-6 and tumor necrosis factor alpha (TNF-α) (Savastano et al., 2015), high-sensitivity c-reactive protein (hs-CRP) (Choi et al., 2017), CRP (Lang et al., 2008) and IL-10 (Song et al., 2017). However, more experimental and epidemiologic data are needed to better understand the possible mediating role of inflammation in BPA-related metabolic effects.

The albumin:creatinine ratio (ACR) is considered a biomarker of early endothelial dysfunction in both children and adults (Bartz et al., 2015). In NHANES, childhood urinary BPA concentrations were cross-sectionally associated with higher urinary ACR levels (Trasande et al., 2013). Another cross-sectional analysis among Chinese adults found similar associations between urinary BPA and a higher risk of low-grade albuminuria (Li et al., 2012). Interestingly, a recent pilot study detecting more BPS than BPA concentrations in children's urine, found that BPS but not BPA concentrations were associated with a higher urinary ACR (Kataria et al., 2017). The ACR should be further studied as a potential biomarker of BPA-related endothelial dysfunction.

Beyond its skeletal effects, vitamin D receptors have been found in many tissues, including the cardiovascular, immune, and reproductive systems (Norman, 2008). In NHANES, higher urinary BPA concentrations were cross-sectionally associated with reduced vitamin D levels in women but not in men (Johns et al., 2016). Maternal prenatal urinary BPA was also associated with reduced maternal serum vitamin D levels and a higher risk of deficiency (Johns et al., 2017). Additionally, among patients with chronic obstructive apnea, serum BPA concentrations were negatively associated with serum vitamin D levels (Erden et al., 2014a). Further studies are warranted to understand the possible interaction between bisphenols and altered levels of the so-called "hormone D" (Norman, 2008).

3.1.2.5. Allergy/Immune biomarkers. Immunoglobulin (Ig)E and specific IgE antibodies play an important role in allergic (atopic) processes including asthma (Froidure et al., 2016). A prospective study among Taiwanese children assessed urinary BPA and serum IgE at 3 and

6 years of age (Wang et al., 2016b). Higher BPA concentrations at age 3 were cross-sectionally associated with increased IgE levels, particularly in girls. Similar results were found at age 6. BPA concentrations at age 3 were prospectively associated with increased IgE levels at age 6. Additionally, IgE levels mediated 70% of the total effect of BPA on asthma risk (Wang et al., 2016b). In NHANES, urinary BPA was positively associated with allergic asthma in adult females, and with sensitization to various specific allergens in a dose–response manner (Vaidya and Kulkarni, 2012). On the contrary, maternal first-trimester urinary BPA concentrations were non-linearly associated with cord blood IL-33 and thymic stromal lymphopoietin (TSLP), but not IgE levels, in a Canadian mother–child cohort (Ashley-Martin et al., 2015). The possible mediating role of both total and specific IgE antibodies in BPA-related allergic sensitization should be further explored.

3.2. Prioritization of effect biomarkers in HBM studies

A wide range of existing bisphenol-related effect biomarkers were identified for most of the human health outcomes screened. Those biomarkers with potential application in HBM studies and supported by mechanistic knowledge organized under the AOP framework were prioritized. First, we discussed the advantages of assessing KiSS and gene expression of nuclear receptors in relation to reproductive effects based on a previously published BPA-related AOP (Viguié et al., 2018). Second, given that biomarkers of brain function were identified as the most important knowledge gap, but no previous BPA-related AOP was available in this area, we built a network integrating mechanistic information on BDNF from three fully-developed AOPs, additionally identifying the pathways through which BPA could lead to altered BDNF function.

3.2.1. Reproductive effect biomarkers

Previous studies have observed significant associations between bisphenols exposure and altered reproductive hormone levels (Suppl. Table 4). However, in many cases the interpretation is hindered by diurnal variations in steroid levels, sets of hormones analyzed, analytical techniques used, periods of exposure and feedback loop effects. The implementation of other complementary effect biomarkers at different levels of biological organization could therefore help to achieve a broader and more accurate picture. A recent evidence-based AOP has exhaustively underpinned the endocrine pathways through which female developmental and/or adult BPA exposure may alter estrous cyclicity, thus increasing the risk of adverse fertility and birth outcomes (Viguié et al., 2018).

Fig. 3 synthesizes and depicts the endocrine pathways and tissues potentially disrupted by BPA exposure in females, adapted from Viguié et al. (2018). Briefly, BPA has been consistently shown to reduce aromatase activity in Granulosa cells, thus preventing the preovulatory rise of estrogens at the ovary (Peretz et al., 2014; Viguié et al., 2018). Additionally, BPA has been shown to act at a central level, interfering with the function of Kisspeptinergic neurons, delaying or suppressing the gonadotrophin-dependent peak of LH needed to achieve ovulation as shown in both rodents and primates (Kurian et al., 2015; Ruiz-Pino et al., 2019; Viguié et al., 2018). Thus, BPA might alter estrous cyclicity and ovulation acting locally in the ovary, centrally in the hypothalamus, or both.

In HBM studies, measuring KiSS protein levels in serum, together with traditional hormone markers (LH, FSH, E2 and TT) may allow a better characterization of potential BPA actions on the HP axis (Fig. 3). Serum KiSS levels could also help to identify the menstrual period in which the sample was taken (Zhai et al., 2017). Similar to other effect biomarkers, particular attention must be given to the storage of samples under the best conditions in order to avoid a potential degradation of this protein over time (Gejl et al., 2019). In addition, evaluating KiSS at other biological levels with higher stability over time, such as for example DNA methylation of *KISS1* in peripheral blood mononuclear cells (PBMCs), could help to counteract the variability related to circulating levels. KiSS plays a crucial role during pregnancy and puberty onset, but also during adulthood regulating the ovulatory mechanism (Cortés et al., 2015). Emerging data is also showing a cross-talk between adipose tissue and kisspeptinergic neurons mediated through the adipokine leptin (Cortés et al., 2015). Overall, KiSS represents an understudied but promising effect biomarker of both reproductive and metabolic health.

Apart from fertility clinic settings in which human oocyte retrieval and follicular fluid sampling is possible (Machtinger et al., 2013), assessing whether BPA may decrease aromatase activity in the ovary is not possible in HBM studies using non-invasive matrices. Notwithstanding, the gene expression and/or DNA methylation of estrogenic receptors [estrogen receptor (ER)α, ERβ, estrogen-related receptor (ERR)α, etc.] and perhaps other molecular targets in blood cell populations could help to evaluate the biological plausibility of BPA associations as previously shown (Melzer et al., 2011), especially when complemented with the abovementioned set of reproductive biochemical biomarkers. Indeed, aromatase gene expression in peripheral blood leukocytes from adult women was significantly higher during the follicular phase compared to the luteal phase of the menstrual cycle, and its expression was correlated with circulating E1 and E2 serum levels (Vottero et al., 2006). Thus, aromatase expression in women's blood could represent an interesting surrogate of local aromatase expression in the ovary. Future studies should investigate whether the expression and epigenetic status of molecular markers in PBMCs is predictive of adverse health effects in human populations.

3.2.2. Neurodevelopmental/neurological effect biomarkers

The neurotrophin BDNF is a promising effect biomarker that could fill an important knowledge gap regarding neurodevelopmental outcomes associated with bisphenols exposure. However, organized data on potential mechanistic pathways that could lead to altered BDNF levels (and other targets) are needed to support its implementation in HBM studies, as well as identify potential novel molecular markers of brain function. Fig. 4 shows the result of integrating three fully-developed AOPs sharing the key event "reduced BDNF release" leading to the same AO: impaired learning and memory. Numbers inside boxes correspond to scientific articles referenced below.

In AOP 54, BPA may decrease TH levels through mechanisms involving the sodium/iodide symporter (NIS) and thyroperoxidase (TPO) as illustrated by reduced iodide uptake through non-competitive inhibition of NIS (Wu et al., 2016) [number 11 in Fig. 4] and decreased mRNA levels of *Nis* and *tpo* (Silva et al., 2018) [12] in rat thyroid follicular cell lines, and decreased TPO activity and NIS-mediated thyroid radioiodide uptake in BPA-exposed rats (Silva et al., 2018). Nevertheless, Silva et al. (2018) reported increased serum T4 levels, which contradicts expected effects in this AOP and other studies showing decreased T4 levels in pregnant ewes and their offspring (Viguié et al., 2013) [13] and aged mice with learning and memory deficits following pubertal exposure (Jiang et al., 2016) [14].

AOPs 12 and 13 describe causal events initiated by inhibition of glutamate N-methyl-D-aspartate receptors (NMDARs). AOP 13 focuses on KEs occurring during brain development and AOP 12 adds downstream events during aging. Reduced hippocampal mRNA and/or protein expressions of NMDAR subunits along with negative effects in different forms of learning and memory were reported in male offspring mice (Xu et al., 2010) [1] and rats (Wang et al., 2014) [2] prenatally exposed to BPA; in mice of both sexes following prenatal and postnatal exposure (Tian et al., 2010) [5]; and in mice exposed postnatally (Jardim et al., 2017) [4].

A single neonatal dose of BPA in mice may reduce hippocampal levels of Calcium/calmodulin-dependent kinase II (CaMKII), a protein activated by calcium influx and crucial for learning and memory (Viberg and Lee, 2012) [15]. In addition to impaired learning and memory, prenatal exposure to BPA decreased hippocampal levels of

phosphorylated cAMP response-binding element (CREB), known to be triggered by Ca2 + influx (Tao et al., 1998), and its target BDNF in male rats (Wang et al., 2016a) [17], and decreased mRNA levels of NMDAR2B and BDNF in male mice (Kundakovic et al., 2015) [16]. Importantly for HBM purposes, BDNF CpG methylation profiles in mice blood reflected methylation profiles and transcription levels in the hippocampus, suggesting that blood BDNF DNA methylation may be a valid surrogate marker of human brain BDNF expression levels (Kundakovic et al., 2015) [16].

As expected from BDNF's critical role in dendritic arborization and synaptic plasticity (Kowiański et al., 2018), decreased dendritic spine density in region CA1 of the hippocampus (critical for memory formation) was reported in rats following postnatal exposure to BPA (Bowman et al., 2014) [8] and in neonates of non-human primates exposed *in utero* (Elsworth et al., 2013) [6]. Prenatal exposure also reduced the length and number of dendritic branches of postnatal mice, with long-term effects consisting of reduced spine densities in hippocampal CA1 of aged mice (Kimura et al., 2016) [9]. Inhibition of NMDAR1, decreased synaptic proteins (e.g., PSD-95, synapsin I, synaptophysin or spinophilin) and altered synaptic structure were observed in the hippocampus of male mice exposed perinatally (Xu et al., 2013) [7], and rats exposed prenatally (Wang et al., 2014) [2]. Furthermore, perinatal exposure reduced expression of synaptophysin and the excitatory to inhibitory synaptic protein ratio in the hippocampus and cortex of male mice (Kumar and Thakur, 2017) [3].

In turn, neuronal network function as evaluated by electrophysiological techniques may be compromised. BPA decreased the induction of hippocampal long-term potentiation (LTP) in juvenile rats together with reduced NMDAR-mediated postsynaptic current in hippocampal slices. Moreover, consistent with inhibited NMDARs, decreased spine density and pre-synaptic glutamate release, spatial memory was impaired (Hu et al., 2017) [10].

In addition to fewer neurons in various regions of the hippocampus, decreased hippocampal LTP induction and impaired learning and memory, Zhou et al. (2017) [18] demonstrated a dose-dependent DNA damage in adolescent male mice brains after chronic exposure. BPA treatment also reduced the viability of hippocampus-derived neural stem cells and induced apoptosis and neurodegeneration in the hippocampus of rats exposed perinatally (Tiwari et al., 2015) [19] and postnatally with deficits in memory and learning (Agarwal et al., 2015) [20]. The contribution of neuroinflammation to the neurodegenerative effects of BPA is substantiated by increased numbers of microglia in the dentate gyrus of both postnatal rats and adult female voles exposed during early development (Rebuli et al., 2016) [21]. Furthermore, maternal BPA increased microglial and astrocyte activation and elevated TNF-α and IL-6 levels in the prefrontal cortex of female offspring mice (Luo et al., 2014) [22].

Several potential biomarkers of effects related to the aforementioned KEs may be relevant for HBM studies. For instance, in seven year old girls, buccal DNA methylation levels of the gene encoding NMDAR2B were positively associated with prenatal urinary BPA concentrations (Alavian-Ghavanini et al., 2018). Specific protein 4 (SP4), a key regulator of NMDAR signaling (Priya et al., 2013), has been proposed as a biomarker of early stage psychosis (Fusté et al., 2013; Pinacho et al., 2015), being a sensitive target of BPA exposure *in vivo* (Lam et al., 2011). Additionally, glial cell-derived neurotrophic factor (GDNF) plays an important role in various neuropsychiatric disorders (Ibáñez and Andressoo, 2017) and may be modulated by BPA along with alterations of dopamine and serotonin systems in rats (Castro et al., 2015). Finally, synapsin I, an important protein for neurotransmitter release and synaptic function exhibited similar expression patterns in both PBMCs and the hippocampus of rats and may serve as an early biomarker of cognitive function (Cifre et al., 2018).

Fig. 4 integrates the pathways presented in the three selected AOPs; however, other mechanisms not covered in those AOPs may also be important. For example, NMDAR inhibition plays a fundamental role in this network as a MIE, but also as a KE when regulated *via* nuclear ERs in the hippocampus (El-Bakri et al., 2004). Indeed, ERs colocalize to cells that express BDNF (Sohrabji and Lewis, 2006), and previous experimental evidence suggests that BPA actions in the hippocampus may be mediated by altered estrogenic signaling (Chen et al., 2017; Leranth et al., 2008). Thus, BPA could lead to altered BDNF function through at least two MoAs: disruption of thyroid and estrogenic pathways. At an HBM level, evaluating a combined set of effect biomarkers implicated in this AOP network (mainly THs and BDNF) could better characterize the neurological effects of bisphenols. Moreover, these targets should be

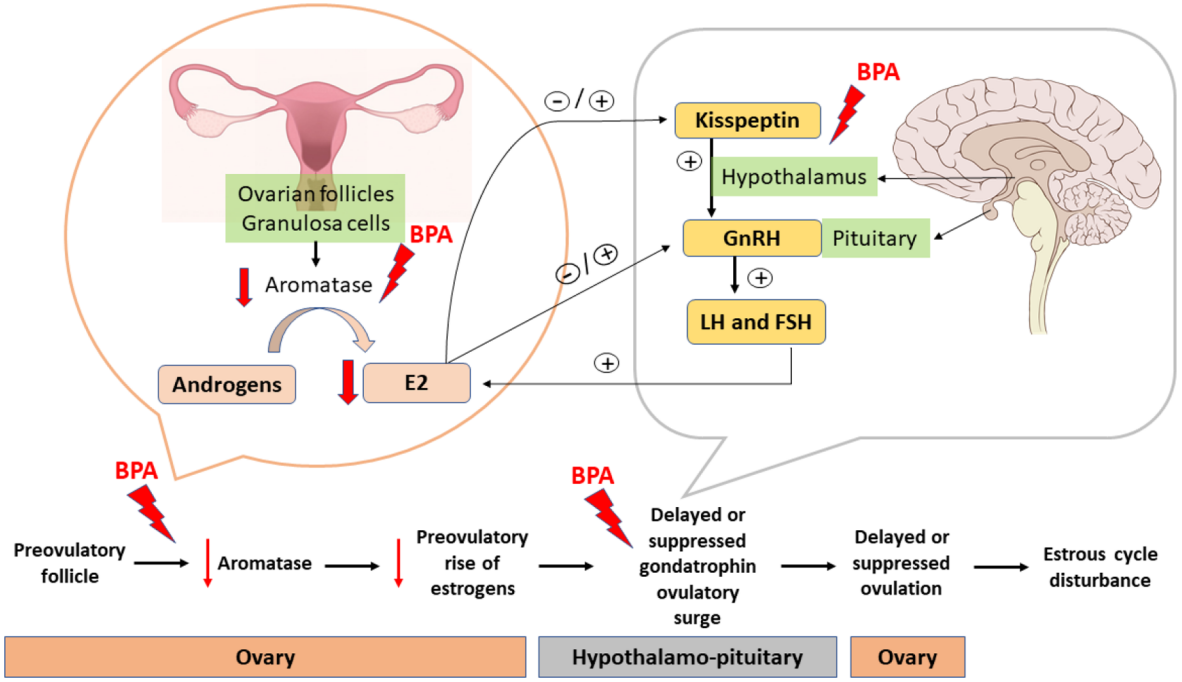


Fig. 3. Hypothesized sequential cascade of BPA events leading to development of altered estrous cycle, adapted from AOP data constructed by Viguié et al. (2018). BPA (bisphenol A); E2 (17β-estradiol); GnRH (gonadotropin-releasing hormone); LH (luteinizing hormone); FSH (follicle stimulating hormone).

assessed at different levels of biological organization (protein levels, gene expression, DNA methylation, etc.) to achieve the most complete picture possible.

A limitation of this AOP network is that the three available AOPs focused on learning and memory, while no AOPs discussing the role of BDNF on behavioral and psychiatric diseases were retrieved from the AOP-Wiki. It's known that BDNF also plays a role in the development of anxiety, depression and mood disorders (Martinowich et al., 2007), and previous reviews of the epidemiologic evidence found that prenatal BPA exposure is associated with behavioral problems in children (Ejaredar et al., 2017; Mustieles et al., 2015; Rodríguez-Carrillo et al., 2019). Therefore, the role of neurotrophins as potential mediators of bisphenol-related actions on behavioral and emotional problems should be also considered in future epidemiologic studies.

4. Conclusions and future perspectives

This comprehensive literature search has allowed us to create the first inventory of existing effect biomarkers for bisphenols, but also to propose potential novel effect biomarkers that may be implemented in HBM studies. The assessment of mechanistically-based effect biomarkers will help to improve the inference of causal relationships between bisphenols exposure and adverse health outcomes in future HBM and epidemiologic studies. Moreover, parallel efforts for other chemical families are ongoing under the HBM4EU initiative (Baken et al., 2019), which will result in a structured body of work that will enable a more systematic approach for the selection of effect biomarkers in the context of exposure to low-dose complex chemical mixtures. This work will also help to prioritize the selection of effect biomarkers for BPA substitutes, facilitating the evaluation of potential adverse effects in a timely manner, without the need to wait for decades until the onset of an overt developmental or chronic disease state.

As a technical limitation, harmonization of measurement methodologies for effect biomarkers in HBM studies is needed, including the performance of interlaboratory comparisons and quality controls, to avoid variability and misclassification errors, thus improving comparison and replicability among studies. The development of analytical methodologies relying on hyphenated mass spectrometry should be encouraged to progressively substitute ELISA and other immunoassays commonly employed. In relation to BPA exposure assessment, many -although not all- of the studies reviewed in this work measured total BPA (free and phase II conjugates) in urine samples using previously validated hyphenated mass spectrometry methodologies following quality assurance and control (QA/QC) measures. In this regard, the HBM4EU initiative has fostered an extensive network of European laboratories that share QA/QC procedures and undergo interlaboratory comparisons to warrant the highest standards for the biomonitoring of exposure to priority compounds. At an epidemiological level, prospective designs with repeated measurements for both exposure and effect biomarkers need to progressively replace cross-sectional studies with only punctual assessments. In addition, future studies should include the implementation of effect biomarkers as potential mediators in the exposure-disease continuum, as a complementary tool to better evaluate exposure-health associations.

Because environmental contaminants such as bisphenols have complex MoA, implementation of effect biomarkers at different levels of biological organization (e.g., DNA, RNA, proteins or metabolites) seems necessary. This point is reinforced considering that, depending on the dose, the target tissue or the window of exposure, the MIE and downstream events may be different. In this review, we proposed to follow the AOP framework for prioritizing the right set of effect biomarkers to be studied. However, there is a limited number of fully developed AOPs. Consequently, efforts are needed to develop more AOPs for many endpoints and xenobiotics, which is another objective of the HBM4EU initiative. The biomarker paradigm and AOP framework (Figs. 1 and 2) have been followed in this review to provide a practical and visual conceptualization to advance the field of effect biomarkers. Although this structured framework presents many strengths, we acknowledge inherent limitations such as the potential existence of non-monotonic dose–response relationships, the inability to assess dose at target organs, and the difficulty of assessing combined effects in the context of complex chemical mixtures.

In future HBM studies, the combined use of multi-omics technologies to perform global characterization of genes (genomics), genome

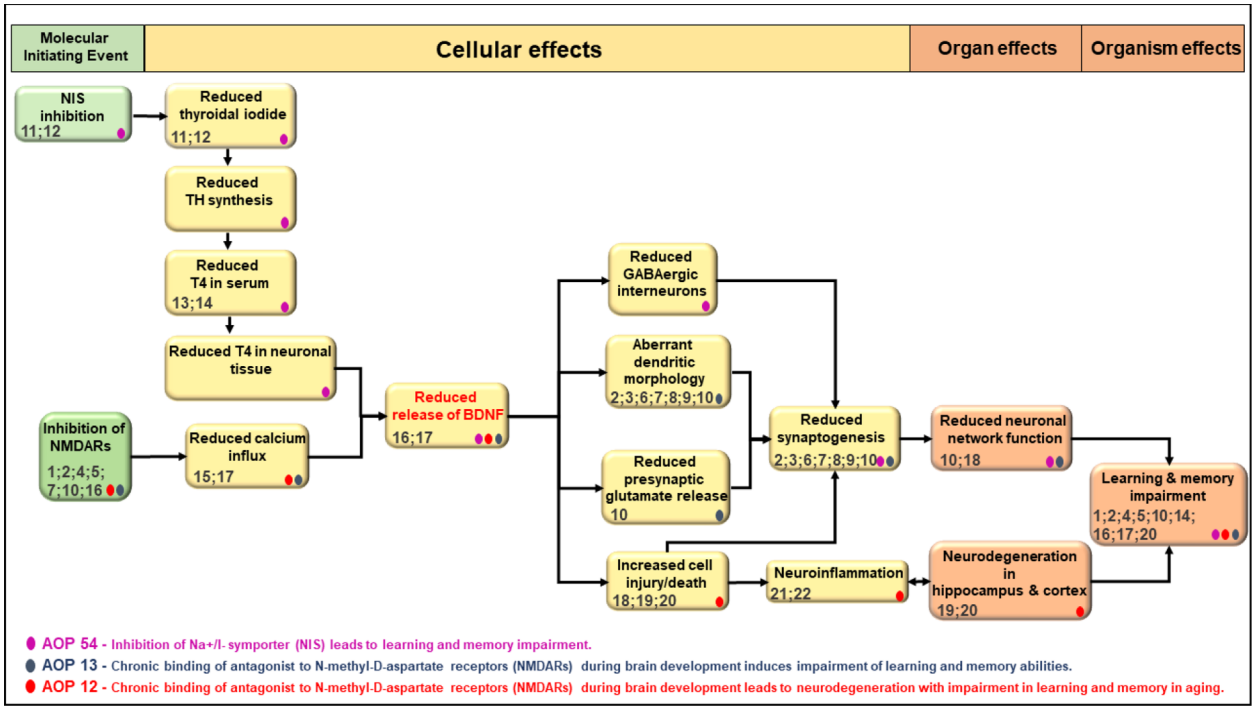


Fig. 4. Network integrating MIEs and KEs from AOPs 12, 13 and 54 leading to a reduced release of BDNF (Boxes), and identification of the steps that can be triggered or promoted by BPA based on available mechanistic data (numbers inside boxes indicate scientific articles referenced in the manuscript).

wide epigenetics, mRNA (transcriptomics), proteins (proteomics) and metabolites (metabolomics) in a specific biological sample seems a very good option to overcome the limitation of looking at the wrong biological level of organization, or the wrong biological targets. Although these technologies are still expensive and require expertise to analyze and interpret the tremendous amount of data generated, systems biology is expanding at a fast rate and the corresponding computational tools are expected to be developed. Moreover, multi-omics should be able to explain complex biological phenomena not only for a class of xenobiotics but for multiple stressors. Hence, untargeted analyses should be encouraged, preferably coupled to targeted analyses, in order to uncover the right biological pathways disrupted by xenobiotics, and their corresponding sets of effect markers.

There is an increasing need to rapidly evaluate the safety of exposure to emerging chemicals in human populations. However, many diseases are only triggered after years of chronic exposure to multiple xenobiotics. Therefore, 21st century environmental policymakers may have to consider whether regulation of chemical contaminants should be proactive and informed by changes in molecular profiles predictive of adverse effects, rather than a *sine qua non* reliance on firm health endpoints that may take decades to investigate.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105811.

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