

Systematic review of prenatal exposure to endocrine disrupting chemicals and autism spectrum disorder in offspring

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Abstract

Epidemiological studies, which can have inherent methodological limitations, are used to study the relation between endocrine disrupting chemicals and autism spectrum disorder. The objective is to systematically review the treatment of methodological limitations and assess the quality and strength of the findings in the available literature. The quality and strength of the evidence were evaluated using the Navigation Guide Systematic Review Methodology. The overall quality and strength of the available studies were “moderate” and “limited,” respectively. Risk of bias due to the methodological limitations regarding the exclusion of potential confounding factors and the lack of accuracy of exposure assessment methods were the most prevalent and were also considered to arrive at these results. The omnipresence of endocrine disrupting chemicals, their persistence and bioaccumulation, and the biological plausibility of the association between prenatal exposure to these and later development of autism spectrum disorder highlight the need to carry out well-designed epidemiological studies that overcome the methodological limitations observed in the currently available literature in order to be able to inform public policy to prevent exposure to these potentially harmful chemicals.

Lay abstract

Autism spectrum disorders comprise a complex group with many subtypes of behaviorally defined neurodevelopmental abnormalities in two core areas: deficits in social communication and fixated, restricted, repetitive, or stereotyped behaviors and interests each with potential unique risk factors and characteristics. The underlying mechanisms and the possible causes of autism spectrum disorder remain elusive and while increased prevalence is undoubtable, it is unclear if it is a reflection of diagnostic improvement or emerging risk factors such as endocrine disrupting chemicals. Epidemiological studies, which are used to study the relation between endocrine disrupting chemicals and autism spectrum disorder, can have inherent methodological challenges that limit the quality and strength of their findings. The objective of this work is to systematically review the treatment of these challenges and assess the quality and strength of the findings in the currently available literature. The overall quality and strength were “moderate” and “limited,” respectively. Risk of bias due to the exclusion of potential confounding factors and the lack of accuracy of exposure assessment methods were the most prevalent. The omnipresence of endocrine disrupting chemicals and the biological plausibility of the association between prenatal exposure and later development of autism spectrum disorder highlight the need to carry out well-designed epidemiological studies that overcome the methodological challenges observed in the currently available literature in order to be able to inform public policy to prevent exposure to these potentially harmful chemicals and aid in the establishment of predictor variables to facilitate early diagnosis of autism spectrum disorder and improve long-term outcomes.

Keywords

autism spectrum disorder, developmental neurotoxicants, endocrine disrupting chemicals, prenatal exposure

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Introduction

Autism spectrum disorders (ASDs) comprise a complex group with many subtypes of behaviorally defined neurodevelopmental abnormalities in two core areas: deficits in social communication and fixated, restricted, repetitive, or stereotyped behaviors and interests each with potential unique risk factors and characteristics (American Psychiatric Association, 2013). Autism is known as a spectrum due to the ample variation in the type and severity of symptoms experienced by those affected by the disorder (Ousley & Cermak, 2014) and can be traced back to the early observations of Kanner and Asperger (Asperger, 1944; Kanner, 1968).

Neurodevelopmental disorders such as ASD are increasing in reported prevalence, are costly (Buescher et al., 2014; Horlin et al., 2014; Rogge & Janssen, 2019), can cause lifelong disability and their causes are mostly unknown. About 1 in 59 children, with the male-to-female ratio of 4 to 1, have been diagnosed with ASD (Centers for Disease Control and Prevention, 2018) and while increased prevalence is undoubtable, it is unclear if it is a reflection of diagnostic improvement or emerging risk factors (Street et al., 2018). The underlying mechanisms and the possible causes of ASD remain elusive despite the extensive research performed over the last 10 years (Street et al., 2018; Tareen & Kamboj, 2012).

ASD is a multi-factorial disorder, and several proposed etiological mechanisms have been discussed in the literature. Liability-threshold models have been used in the study of the multi-factorial etiology of ASD (Colvert et al., 2015; Frazier et al., 2014; Robinson et al., 2011; Szatmari et al., 2012; Tick et al., 2016).

Solely genetic factors account for approximately between 20% and 30% of all cases, whereas 70%–80% are the result of the combination of environmental risk factors and some type of genetic susceptibility (Lai et al., 2014). The search for the causes of ASD has been complicated by the contributing role of environmental factors (Berko et al., 2014; Moore et al., 2000; Rasalam et al., 2005; Sandin et al., 2014; St-Hilaire et al., 2012; Tordjman et al., 2014; Volk et al., 2013) which may act during pregnancy (Depino, 2018; Nicolini & Fahnstock, 2018) or other critical stages of development.

One of these possibly contributing environmental factors are endocrine disrupting chemicals (EDCs), a wide range of synthetic compounds with the capacity to disrupt normal neurophysiological mechanisms and interfere with the endocrine system, mimicking the action of endogenous hormones; antagonizing their mechanism of action; altering their pattern of synthesis, transport, release or metabolism; or by modulating the levels of the corresponding receptors (Ghosh et al., 2015). EDCs have been shown to be neurotoxic in laboratory models and epidemiological studies addressing the hypothesis that they are instrumental in the pathogenesis of ASD are increasing. EDCs

deserve consideration as candidate risk factors for ASDs because of their potential to alter hormonal axis functions that play an important role in neurodevelopment.

Exposure to EDCs during critical developmental periods can increase risk for a variety of diseases and can have direct effects on the offspring, as well as impacts much later in life (Barouki et al., 2012). Recent studies have suggested that many complex non-communicable diseases typically experienced in adulthood may have their origin in these critical development periods (Barker, 2012; Barouki et al., 2012; Braun et al., 2009, 2017; Gore et al., 2015; Heindel et al., 2016; Herbstman et al., 2010; Y. Kim et al., 2011; Lee & Jacobs, 2015; United Nations Environment Programme [UNEP] & World Health Organization [WHO], 2013; Vrijheid et al., 2016). Epidemiological studies have found that some prenatal, perinatal, and childhood environmental exposures increase the risk for ASD (Atladóttir et al., 2010; A. L. Roberts et al., 2013; Stoltenberg et al., 2010; Surén et al., 2013; Zerbo et al., 2017).

Based on the currently available published literature, the evidence supporting the causative or etiologic role of endocrine factors in ASD remains sparse, somewhat controversial, and in finality inconclusive. Many studies have tried to establish an etiologic connection between ASDs and the role of endocrine factors, and although an association between endocrine abnormalities and some aspects of ASD has been shown in several of these studies, the results must be interpreted with caution given the complexities involved in ASD and EDC research. Addressing key methodological issues at the study design stage can help to arrive at valid results and even if it is not possible to optimize human study design due to inherent limitations, understanding methodological issues can be useful when interpreting findings from human studies (Lee & Jacobs, 2015).

The objective of this article is to systematically review the treatment of possible methodological limitations related to the study of exposure to EDCs during pregnancy and the later diagnosis of ASD in the offspring in the available literature to aid in the design of future studies to minimize methodological limitations and assess the quality and strength of the findings.

Methods

Search strategy and eligibility criteria

Following the Spanish National Health System recommendations, the search was based on Medline, although these other databases were also consulted: Cochrane Library, Scielo, Scopus, Embase, Google Scholar, PsycINFO, and Web of Science. Table 1 shows the search strategy using the following MeSH terms: *child development disorders*, *pervasive*, *autism spectrum disorder*, *autistic disorder*, *child behavior disorders*, *endocrine*

Table 1. Search strategy.

	Terms
#1	"Autism spectrum disorder" [MeSH] OR "Autistic disorder" [MeSH] OR "Child Development Disorders, Pervasive" [MeSH] OR "Child Behavior Disorders" [MeSH] OR "autistic traits"
#2	"Environmental Exposure" [MeSH] OR "Endocrine Disruptors" [MeSH] OR "Pesticides" [MeSH] OR "Polychlorinated Biphenyls" [MeSH] OR "Hydrocarbons, Chlorinated" [MeSH] OR "Dichlorodiphenyl Dichloroethylene" [MeSH] OR "DDT" [MeSH] OR "Hexachlorobenzene" [MeSH] OR "Flame Retardants" [MeSH] OR "Polybrominated Biphenyls" [MeSH] OR "Perfluorooctane sulfonic acid" [Supplementary Concept] OR "Bisphenol A" [Supplementary Concept] OR "Perfluorooctanoic acid" [Supplementary Concept]
#3	"pregnancy" OR "prenatal" OR "in utero"
#4	#1 AND #2 AND #3

disruptors, environmental exposure, pesticides, pregnancy, prenatal, and "in utero" with the corresponding Boolean operators.

Original articles published from 2005 to May 2018 were searched. The 2005 cutoff date was considered appropriate because the increasing ASD prevalence of ASD registered (Centers for Disease Control and Prevention [CDC], 2007, 2012) and because the potential negative effects of EDCs have not been examined until recently. Studies that met the following criteria were included (1) contained original data; (2) were observational (i.e. cohort, case-control, ecological, or cross-sectional); (3) included subjects without restriction of any demographic characteristics of the population (mainly racial or ethnic restrictions); (4) the exposure was measured during pregnancy; (5) the EDC exposure was measured either: (a) through questionnaires/interviews held with parents, (b) estimations provided by environmental agencies, or medical reports, and (c) analyses of biological samples; and (6) the outcome was ASD diagnosis.

Papers classified as review articles; hypothesis papers; individual medical case studies; theses/dissertations; conference papers; and letters to the editor were excluded from the search. This exclusion follows previously used methodologies (see: Friedenreich, 1993; Froom & Froom, 1993) and conforms to the approach outlined in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart (Liberati et al., 2009).

Data extraction

A first screening based on title and abstract was conducted by two different groups of reviewers (S.M.-B., C.D.-V., A.M.-S. and M.M.S.-V., I.P.-C., A.L.-G., J.L.-M.). Next, two reviewers with expertise in the fields of epidemiology and environmental health conducted a full-text selection based on the eligibility criteria. The resultant studies were compared to determine agreement for the inclusion criteria and descriptive information was collected. After this discussion, agreement was obtained on 100% of articles.

Literature research

The Navigation Guide Systematic Review Methodology (Woodruff et al., 2011; Woodruff & Sutton, 2014) was applied to review, synthesize, and rate the quality and strength of the available scientific evidence. The application of the Navigation Guide was guided by a detailed four-step protocol developed around the "PECO" (population (P), exposure (E), comparator (C), and outcomes (O) of interest) statement (Morgan et al., 2018) which in turn is based on the Cochrane "PICO" (patient, problem, or population (P), intervention (I), comparison or control (C), and outcome (O) of interest) statement (The Cochrane Collaboration, 2011).

According to the PECO statement, the four areas to take into account in this review were (1) populations of interest: pregnant women and their children of any age; (2) exposures: to EDCs during pregnancy, measured directly from biological samples, estimated through questionnaires/interviews or provided by environmental agencies; (3) comparators: prenatal exposure to EDC (exposure range comparison) of children with ASD versus those without (control group); and (4) outcomes: children of any age with clinical ASD diagnosis. Which in turns translates into the following Navigation Guide protocol steps: (1) specify the study question (Is developmental exposure to endocrine disrupting chemicals during pregnancy associated with a subsequently increased risk for the later diagnosis of ASD in children?); (2) select the evidence; (3) rate the quality and strength of the evidence; and (4) grade the strength of the recommendations (Step 4 was not addressed in this study because of the limitations of our resources).

Internal validity assessment

To support any judgment of bias risk in each study, a pre-determined review protocol was completed adapting a pre-existing protocol (see Supplemental protocol). This pre-existing protocol is available on the International Prospective Register of Systematic Reviews (PROSPERO) (Lam et al., 2015). In making determinations of the risk of bias, the following domains were considered for each

study: recruitment strategy; blinding; confounding; exposure/outcome assessments; incomplete outcome data; selective outcome reporting; conflict of interest; and any other biases (Lam et al., 2015, 2016).

Within the other bias domain and prior to the evaluation of studies, the coauthors collectively developed the following list of potentially important factors that did not fall within the other domains studied: socio-economic status, residence, parental age, and season of conception/birth. It must be highlighted that these factors can act as direct confounders and could potentially also be included in this domain. However, in some cases, they may not affect both the exposure and the outcome, and therefore may not be strictly labeled as confounders. Taking this into consideration, it was determined that while their influence on at least the exposure or the outcome does not necessarily warrant their inclusion in the risk of bias assessment as their omission from the analysis may not induce bias and in some situations, especially when the factor is strongly associated with only the exposure, their inclusion may make the analysis less efficient and thus be unwarranted, their inclusion should be considered on an individual basis. This list of potential factors that may affect bias served as a guide during the study assessment process but should not be understood as a hard checklist of covariates that must always, a priori, be accounted for in any given analysis to prevent bias. This assessment was individualized for each study; therefore, the factors considered under the “confounding” and “other” domains vary depending on the study. When a specific factor acts as a confounder, they are assessed in the “confounding” domain and when they do not meet the criteria of confounder they are included in the “other” domain.

There are other covariates that could have also been included in the determination of bias but have been, after consideration, been included in other specific domains even if in some cases they may have impacted the risk of bias, and further information can be found in the Supplemental protocol. A specific example of this related to exposure assessment would be whether the gestational age of the participants was specified. This was considered for all studies given the importance of the timing of exposure when studying EDCs. While a lack of information of the timing of exposure may not necessarily bias the analysis itself, it may inhibit the ability to look at effects of exposure at specific windows of susceptibility, therefore providing an incomplete picture. Also, in the specific domain of exposure assessment, and according to the pre-established protocol, in general, studies that used indirect exposure measurements, or less established estimates of exposure, were rated as being at a higher risk of bias. In the case of air quality monitoring stations or historical emissions databases, the risk of bias was rated as lower and it must be noted that in some cases the use of proxy measures can be better than using more personal measures (Weisskopf & Webster, 2017).

Quality and strength of the evidence

The Navigation Guide methodology for conducting a systematic review in the clinical sciences follows the approach established by the Grading of Recommendations Assessment Development and Evaluation (GRADE) (Balslem et al., 2011; Guyatt, Oxman, Akl, et al., 2011; Guyatt, Oxman, Kunz, et al., 2011; Guyatt, Oxman, Vist, et al., 2011), method where a pre-specified a priori “moderate” quality rating was assigned to each study and to the overall body of evidence. Then, the quality of the human evidence was accounted for through adjustments (“downgrades” or “upgrades”) to the quality rating based on the characteristics of the included studies as described in Table 2. These adjustment factors that were used to assess the overall body of evidence for downgrading and upgrading the pre-specified quality ratings were taken from GRADE guidelines and are risk of bias, inconsistency, indirectness, imprecision, publication bias, magnitude of effect, dose-response, and confounding.

The rating categories for the overall strength of the evidence specified in the Navigation Guide (“sufficient evidence of toxicity,” “limited evidence of toxicity,” “inadequate evidence of toxicity,” or “evidence of lack of toxicity”) were adapted from degrees of certainty provided by the US Preventive Services Task Force (Sawaya et al., 2007), the International Agency for Research on Cancer (IARC; 2006), and the US Environmental Protection Agency (USEPA; 2016) for evidence integration (Table 3). The overall strength of each body of evidence rating was based on four considerations: quality of body of evidence; direction of effect; confidence in effect; and other compelling attributes of the data that may influence certainty.

The final overall quality and strength of the evidence were independently evaluated by the five reviewers. Finally, the evaluations were compared, the discrepancies were discussed, and the final decisions were justified collectively. Members of the autistic and autism communities were not involved in the study.

Results

A total of 251 unique studies were retrieved using chosen search terms and screened for relevance after removing duplicates. Twenty-five of those publications met the inclusion criteria, and included ecological, cross-sectional, case-control, and cohort study designs (Figure 1).

Data collection methods of the exposure to EDCs varied across the studies. To take into account the different methodologies used to measure the EDC exposure, the studies were grouped based on the methodology used for assessment of the exposure: ten (40%) used questionnaires/interviews or from medical records (Table 4), nine (36%) based estimations on information provided by environmental government agencies from air quality monitoring stations or historical emissions (Table 5), and six (24%) used biological samples (Table 6).

Table 2. Criteria for assigning quality and strength of evidence to observational studies (Woodruff et al., 2011).

Risk of bias ^a	Quality of evidence ^b	Strength of evidence ^b
Domains: Recruitment strategy Blinding Confounding Exposure assessment Outcome assessment Incomplete outcome data Selective outcome reported Conflict of interest Other bias Determinations: Low risk Probably low risk Probably high risk High risk	Human evidence begins as moderate Downgrade criteria (-1 or -2): Risk of bias Inconsistency of results Indirectness of evidence Imprecision Publication bias Upgrade criteria (+1 or +2): Magnitude of effect Dose-response Confounding Rating: High Moderate Low	<i>The final rating represents the level of certainty of toxicity.</i> Considerations: Quality of body evidence Direction of effect Confidence in effect Other compelling attributes of the data that may influence certainty Rating: Sufficient Limited Inadequate Lack of association

^aDetermined for each individual study.^bRated across all studies.**Table 3.** Strength of evidence of association.

Strength rating	Definition ^a
Sufficient	A causal relationship has been established between exposure and outcome where chance, bias, and confounding can be ruled out with reasonable confidence. The available evidence includes results from one or more well-designed, well-conducted studies, and the conclusion is unlikely to be strongly affected by the results of future studies.
Limited	A positive association is observed between exposure and outcome for which a causal interpretation is considered to be credible but chance, bias, and confounding cannot be ruled out with reasonable confidence. Confidence in the relationship is constrained by such factors as: the number, size, or quality of studies, or inconsistency of findings across individual studies. Future studies could change the observed effect and consequently alter the conclusion.
Inadequate	The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding to presence or absence of a causal association between exposure and outcome. More information may allow an assessment of effects.
Lack of association	Not showing a positive association between exposure and any studied outcome at any observed level of exposure and chance, bias and confounding can be ruled out with reasonable confidence. The conclusion is unlikely to be strongly affected by the results of future studies.

^aThe rating categories were adapted from degrees of certainty provided by the US Preventive Services Task Force Levels of Certainty Regarding Net Benefit (Sawaya et al., 2007), the IARC (2006), and the USEPA (2016) for evidence integration.

In the group of studies that used questionnaires/interviews or from medical records for the collection of data on exposure to EDCs (Croen et al., 2008; Geier et al., 2008, 2009; S. M. Kim et al., 2010; Larsson et al., 2009; McCanlies et al., 2012; Miles & Takahashi, 2007; Pino-López & Romero-Ayuso, 2013; Price et al., 2010; Windham et al., 2013), 8/10 were case-control studies and the remaining two were one a retrospective cohort and the other a cross-sectional study. In these studies, maternal exposures during pregnancy to thimerosal, mercury, polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), bisphenol (BPA), polychlorinated dibenzo-*p*-dioxin (PCDD), phthalates, industrial chemical contaminants, solvents,

exhaust/combustion products, disinfectants, metals, pesticides, cooling fluids, and auto paint were evaluated. The studies can be divided into two main groups: those that studied thimerosal exposure and those that studied maternal occupational exposure. The separation between thimerosal exposure and occupational exposure was made as Rh immune globulin and some vaccines contained the preservative thimerosal until relatively recently in some countries (2001 in the United States, for example). Croen et al. (2008) must be highlighted for having a sample of 400 children diagnosed with ASD, the largest in this group while Miles and Takahashi (2007), Price et al. (2010), and Windham et al. (2013) also had sizable samples of over 200 children

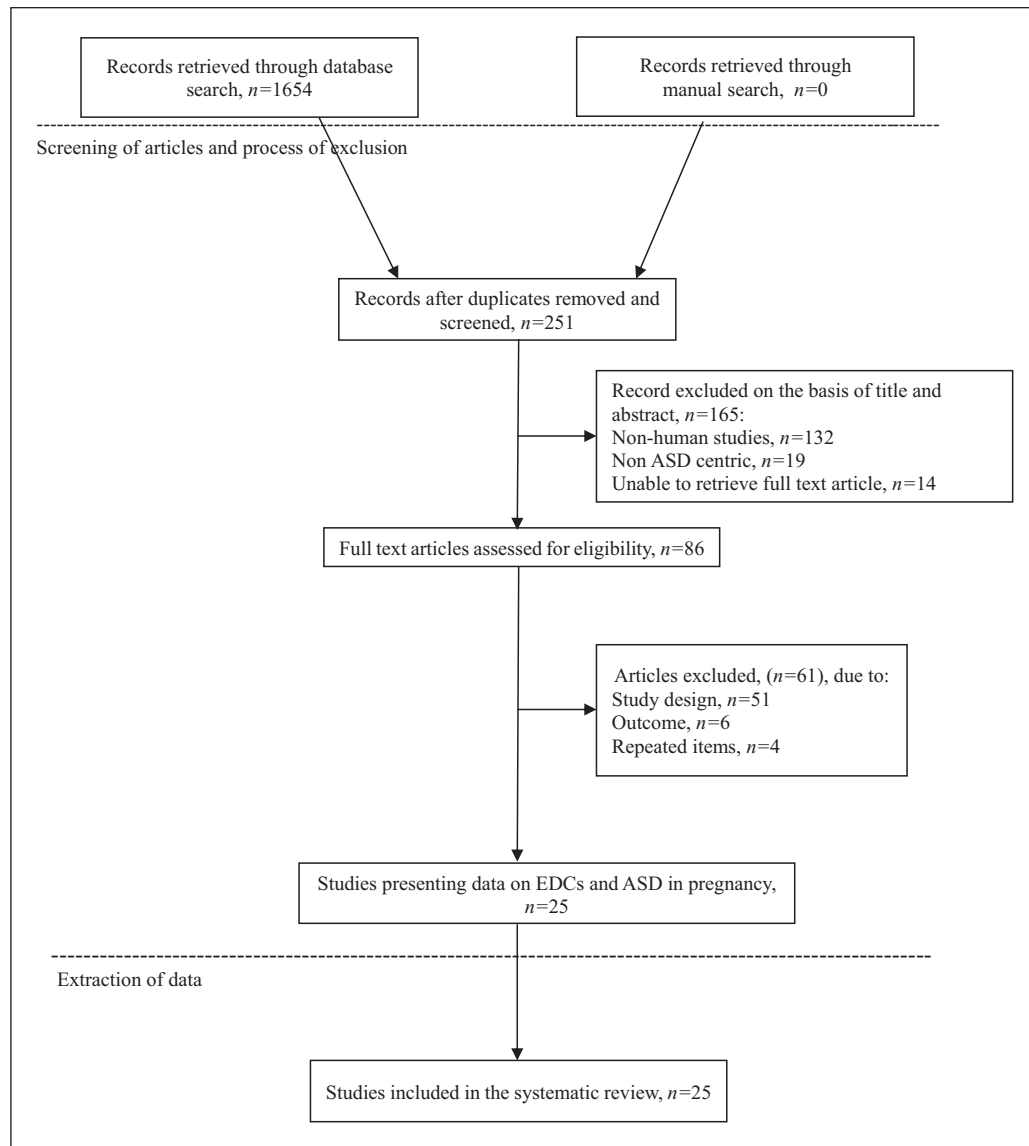


Figure 1. PRISMA flow diagram of the systematic review process.

with ASD. It must be noted that in all cases, the male-to-female ratio is widely eschewed in favor of males which is to be somewhat expected given the difference in diagnosis numbers for each sex. Three studies were carried out on non-US populations: two European (Spain and Sweden) and one Asian (Korea). The *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; DSM-IV-TR) was the most commonly used ASD diagnostic tool; however, Korean-Child Behavior Checklist (K-CBCL), Autism Diagnostic Interview-Revised (ADI-R), Autism Diagnostic Observation Schedule (ADOS), and Modified Checklist for Autism in Toddlers (M-CHAT) were also used and parent-reported ASD was also included in some studies. The results obtained by 6/10 studies show a statistically significant positive association between exposure to the EDCs studied and ASD diagnosis. In the remaining four of the studies, a risk of developing ASD is found, but it is not statistically

significant. It must be noted that three of the four studies that did not find statistically significant risk of developing ASD belong to the group that studied thimerosal.

For the group of studies that based estimations of the exposure to EDCs on information provided by environmental government agencies (Dickerson et al., 2016; Kalkbrenner et al., 2010; A. L. Roberts et al., 2013; E. M. Roberts et al., 2007; Shelton et al., 2014; Talbott et al., 2015; Volk et al., 2011; von Ehrenstein et al., 2014; Windham et al., 2006), 7/9 studies were of case-control designs, one was ecological, and the remaining was a cohort. In these studies, exposure assessment was estimated using data on ambient concentrations of pollutants and proximity to sources of these. The EDCs studied include antimony, arsenic, cadmium, chromium, cyanide, lead, manganese, mercury, nickel, metals, styrene, 1,3-butadiene, benzene, toluene, ethyl-benzene, xylenes,

Table 4. Studies with the estimation of concentrations of endocrine disrupting chemicals provided by parental interview/questionnaires or from medical records.

Author and year	Study population and sample size (N)	Study design	Exposure	Outcome	Results	Risk of bias
Croen et al. (2008)	Four hundred children (330 boys and 70 girls) with ASD and 410 TD children (335 boys and 75 girls), Kaiser Permanente Northern California hospitals.	Observational case-control study	Maternal Rho (D) status and anti-D immune globulin exposure (thimerosal).	ASD status is confirmed using the <i>Diagnostic and Statistical Manual of Mental Disorders</i> (4th ed., text rev.: DSM-IV-TR) criteria.	ASD: aOR = 1.1 (95% CI = 0.64–1.80) for maternal Rh negative status and aOR = 1.03 (95% CI = 0.60–1.76) for exposure to anti-D immune globulin (thimerosal).	Recruiting strategy: probably low Blinding: probably low Confounding: probably high Exposure assessment: probably high Outcome assessment: probably high Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: low
Geier et al. (2008)	Ninety-two ASD patients (80 boys and 12 girls) and 124 TD children (54 boys and 70 girls) (Lynchburg, VA). 87 ASD patients (76 boys and 11 girls) and 1021 pregnant women (Rockville and Baltimore, MD).	Case-control study	Maternal negative Rho (D) status prenatal and Rho(D)-immune globulin exposure (thimerosal).	Non-specified ASD status.	Clinic A: OR = 2.9 (95% CI = 1.3–6.2). Clinic B: OR = 2.5 (95% CI = 1.1–5.5).	Recruiting strategy: high Blinding: probably low Confounding: high Exposure assessment: probably high Outcome assessment: high Incomplete outcome data: probably high Selective outcome reporting: probably low Conflict of interest: high Other bias: probably high
Geier et al. (2009)	Hundred pregnant mothers and corresponding children (85 boys and 15 girls) with ASD from Genetic Centers of America. Prospectively recruited using convenience sample.	Cross-sectional study	Self-reported number of dental amalgams (exposure to mercury) in pregnant mothers.	All children were diagnosed with DSM-IV criteria and clinical observation with ATEC.	3.2-fold increased risk of ASD severity among those children whose mothers had ≥6 dental amalgams during pregnancy compared to those with <5.	Recruiting strategy: high Blinding: low Confounding: high Exposure assessment: probably high Outcome assessment: probably high Incomplete outcome data: probably high Selective outcome reporting: probably low Conflict of interest: high Other bias: probably high
S. M. Kim et al. (2010)	Hundred and six mothers of children with ASD (71 boys and 35 girls) and 324 mothers of TD children (203 boys and 121 girls) were recruited from special and elementary schools, respectively, in Seoul, Chungju, and Chuncheon, South Korea.	Observational case-control study	Self-reported exposure. Two questionnaires (knowledge/exposure) asking about the potential risk to EDCs. These questions regarding possible exposure to PBDEs, PCBs, BPA, and PCDD were selected based on the guidelines provided by the study "Ministry of Environment for the Republic of Korea."	The Child Behavior Checklist Korean version (K-CBCL) was used to assess the diagnosis and severity of behavioral traits of ASD in children.	The knowledge regarding the possible toxicity to EDCs, such as PBDEs, PCBs, BPA, and PCDD was significantly higher in cases than controls ($t = 2.9, p = 0.001$) and self-reported exposure was significantly higher in cases than controls ($t = 5.6, p = 0.001$).	Recruiting strategy: probably low Blinding: probably low Confounding: high Exposure assessment: probably high Outcome assessment: high Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: low
Larsson et al. (2009)	Seventy-two children (60 boys and 12 girls) with ASD in the county of Värmland, Sweden.	Retrospective study based on the DBH longitudinal cohort study	Questionnaire asking for type of floor material used at home (PVC, wood, linoleum, etc.) as source of phthalates.	Parentally reported ASD.	ASD: aOR = 1.66 (95% CI = 1.02–2.7) for children with PVC floor at home in comparison with those with other floor material. Poor ventilation was also associated with ASD.	Recruiting strategy: probably low Blinding: probably low Confounding: high Exposure assessment: high Outcome assessment: high Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: low

(Continued)

Table 4. (Continued)

Author and year	Study population and sample size (N)	Study design	Exposure	Outcome	Results	Risk of bias
McCanlies et al. (2012)	One hundred seventy-four families: 93 children with ASD (82 boys and 11 girls) and 81 TD children (61 boys and 20 girls) born and living in California, and enrolled in the CHARGE study.	Observational case-control study	Industrial-Hygienist Evaluation Exposures, i.e. occupational exposure to asphalt and several solvents including nickel, chromium, iron, aluminum, lead, toluene, xylene, phthalate, and PCBs, and collected retrospectively.	ASD were assessed on ADI-R and ADOS.	Higher exposure ($OR \geq 2$) to asphalt and solvents were observed among parents with ASD children compared with parents of TD children. But no significant associations after correcting.	Recruiting strategy: probably low Blinding: low Confounding: probably low Exposure assessment: high Outcome assessment: low Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: low
Miles and Takahashi (2007)	Two hundred and fourteen cases (ASD) (169 boys and 45 girls) and 3 sub-control groups (65, 12,454, and 160,276 control groups) (Missouri).	Observational case-control study	Maternal negative Rh D status and Rh immune globulin exposure (thimerosal) were obtained from the maternal interview and clinical records.	ASD diagnosed by DSM-IV criteria and ADI-R.	For maternal Rh negative status, OR (95% CI) 1.00 (0.47–2.16) for 65 controls, 1.02 (0.7–1.48) for 12,454 controls, and 0.85 (0.61–1.27) for 160,276 controls.	Recruiting strategy: probably low Blinding: probably low Confounding: probably high Exposure assessment: probably high Outcome assessment: probably low Incomplete outcome data: probably low Selective outcome reporting: probably low Conflict of interest: probably high Other bias: low
Pino-López and Romero-Ayuso (2013)	Seventy children with ASD (59 boys and 11 girls) and 136 TD children (88 boys and 48 girls) evaluated in the Early Intervention Service of Ciudad Real, Spain.	Observational case-control study	Self-reported parental occupation to evaluate exposure to solvents during pregnancy.	ASD were assessed on the M-CHAT.	Mother's job handling of solvents $aOR = 3.89$ (95% CI = 1.08–13.98); if the father handling of solvents $aOR = 3.71$ (95% CI = 1.26–10.92).	Recruiting strategy: low Blinding: low Confounding: probably low Exposure assessment: high Outcome assessment: probably high Incomplete outcome data: low Selective outcome reporting: low Conflict of interest: low Other bias: probably low
Price et al. (2010)	Two hundred fifty-six children with ASD (87 boys and 13 girls) and 752 TD children (85 boys and 15 girls). The Vaccine Safety Datalink Project, USA.	Case-control	Maternal interview on vaccination and Rh immunoglobulin (thimerosal) exposures during pregnancy, and from maternal medical sources.	ASD were assessed on the ADI-R and the ADOS.	Prenatal exposure did not find associations with ASD ($aOR = 1.01$ (95% CI = 0.99–1.03)).	Recruiting strategy: probably low Blinding: probably low Confounding: probably low Exposure assessment: probably high Outcome assessment: low Incomplete outcome data: low Selective outcome reporting: low Conflict of interest: probably high Other bias: probably low

(Continued)

Table 4. (Continued)

Author and year	Study population and sample size (N)	Study design	Exposure	Outcome	Results	Risk of bias
Windham et al. (2013)	Parental occupation was obtained from birth certificates for 284 children with autism and 659 controls, born in 1994 in the San Francisco Bay Area. Parental occupation was obtained from birth certificates for 284 children with autism and 659 controls, born in 1994 in the San Francisco Bay Area. Parental occupation was obtained from birth certificates for 284 children with autism and 659 controls, born in 1994 in the San Francisco Bay Area. Two hundred eighty-four children with ASD (241 boys and 43 girls) and 659 TD children (534 boys and 125 girls), born in 1994 in the San Francisco Bay Area (California).	Observational case-control study	Self-reported occupation and industry exposures are coded by occupational medicine-certified physician into seven chemical groups (exhaust/combustion products, disinfectants, metals, pesticides, solvents, cooling fluids, and auto paint).	Autism cases are identified according the DSM-IV by qualified medical professionals.	Mothers of children with ASD had a higher probability (aOR = 2.3; 95% CI = 1.3–4.2) of working in occupations considered exposed compared to mothers of controls (non-exposed). The exposure categories of the greatest frequency among case mothers were exhaust and combustion products (aOR = 12.0; 95% CI = 1.4–104.6) and disinfectants (aOR = 4.0; 95% CI = 1.4–12.0).	Recruiting strategy: probably low Blinding: low Confounding: probably low Exposure assessment: high Outcome assessment: probably low Incomplete assessment data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: low

ASD: autism spectrum disorder; TD: typically developing; ATEC: Autism Treatment Evaluation Checklist; PBDEs: polybrominated diphenyl ethers; PCBs: polychlorinated biphenyls; BPA: bisphenol A; PCDD: polychlorinated dibenzo-p-dioxin; DBH: dampness in buildings and health; CHARGE: Childhood Autism Risks from Genetics and Environment study; M-CHAT: Modified Checklist for Autism in Toddlers; ADI-R: Autism Diagnostic Interview-Revised; ADOS: Autism Diagnostic Observation Schedule; EDC: endocrine disrupting chemical; aOR: adjusted odds ratio; CI: confidence interval.

Table 5. Studies with the estimation of concentrations of endocrine disrupting chemicals provided by environmental agencies.

Author and year	Study population and sample size (N)	Study design	Exposure	Outcome	Results	Risk of bias
Kalkbrenner et al. (2010)	Three hundred ninety-five children with ASD (323 boys and 72 girls) and 3177 children (1854 boys and 1025 girls) with speech and language limitations in North Carolina and West Virginia.	Case-control study	Exposures to ambient concentrations of metal, particulate, and volatile organic air pollutants in the child's birth residence were assigned from the National Air Toxics Assessment annual-average model.	Cases were all children with developmental records that met a standardized definition for ASD based on the DSM-IV-TR.	OR for beryllium compounds was 1.5 (95% CI = 1.1–2.0) and aOR = 1.0 (0.6–1.4). For xylenes, the OR was 1.5 (1.2–2.0) and the aOR was 1.0 (0.6–1.6). Quinoline aOR = 1.4 (1.0–2.2) and styrene aOR = 1.8 (1.0–3.1).	Recruiting strategy: low Blinding: probably low Confounding: low Exposure assessment: probably low Outcome assessment: probably low Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: probably low
E. M. Roberts et al. (2007)	Four hundred sixty-five children with ASD and 6975 paired TD children (Central Valley, California).	Observational case-control study	Residential proximity of sources of agricultural pesticides: organochlorines and organophosphates assigned by maternal residence at delivery.	Children with ASD were identified through electronic files of the California Department of Developmental Services according to DSM-IV-TR.	In children of mothers living within 500 m of field sites (the fourth quartile vs the lowest non-zero quartile of organochlorine poundage) to those with mothers not living near field sites the aOR was for ASD of 6.1 (95% CI = 2.4–15.3).	Recruiting strategy: probably low Blinding: probably low Confounding: probably low Exposure assessment: probably low Outcome assessment: probably low Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: low
A. L. Roberts et al. (2013)	Three hundred twenty-five children with ASD (46 girls and 279 boys) and 22,101 TD children. From all 50 US states.	Case-control study from the Nurse's Health Study II cohort	US EPA concentrations of several pollutants according to residency: antimony, arsenic, cadmium, chromium, lead, manganese, mercury, nickel, all metals, diesel particulate, styrene, and methylene chloride.	ASD diagnosis validated by telephone administration of the Autism Diagnostic Interview-Revised (ADI-R) to 50 randomly selected case mothers.	Comparing the higher quintile score and the lowest quintile Lead: aOR = 1.6; 95% CI = 1.1–2.3. Manganese: aOR = 1.5; 95% CI = 1.1–2.2. Mercury: aOR = 2; 95% CI = 1.2–3. Nickel: aOR = 1.7; 95% CI = 1.1–2.5. Cadmium: aOR = 1.5; 95% CI = 1.0–2.1. Total metals: aOR = 1.5; 95% CI = 1.0–2.3. Styrene: aOR = 1.4; 95% CI = 1.0–2.1. Methylene chloride: aOR = 1.8; 95% CI = 1.2–2.8. Diesel particulate: aOR = 2; 95% CI = 1.0–4.0.	Recruiting strategy: probably low Blinding: probably low Confounding: probably low Exposure assessment: probably low Outcome assessment: probably low Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: low
Dickerson et al. (2016)	A total of 2558 census tracts from five study sites: 644 from Arizona, 631 from Maryland, 588 from New Jersey, 368 from South Carolina, and 327 tracts from Utah. On average, 81.6% of ASD cases were male.	Ecological study design	It is measured ambient concentrations of lead, mercury, arsenic, and metalloid independently. Additive and synergistic effects of combinations of these metals are also considered. To coincide with the prenatal periods of the children, the corresponding annual data of the Toxic Release Inventory (TRI) for the arsenic, lead, and/or mercury emissions were used.	ASD status is confirmed using <i>Diagnostic and Statistical Manual of Mental Disorders</i> (4th ed., text rev.; DSM-IV-TR) criteria.	Comparing fourth to first quartile of exposures to ambient concentrations: Lead PR (prevalence ratio = 1.36; 95% CI = 1.18–1.57). Census tracts with mercury concentrations in the highest quartile and arsenic concentrations below this quartile had a significantly ASD prevalence (adjusted relative risk (aRR) = 1.20; 95% CI = 1.03–1.40).	Recruiting strategy: low Blinding: probably low Confounding: probably high Exposure assessment: probably high Outcome assessment: probably low Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: high (ecological fallacy)
Shelton et al. (2014)	Four hundred eighty-six children with ASD and 316 TD children (CHARGE study, California).	Case-control study	Proximity of homes to agricultural pesticides is used to estimate pesticide exposure using the Pesticide Use Report (PUR). Pesticides included are organophosphates, carbamates, pyrethroids, organochlorates, and chlorpyrifos.	Children are administered the Autism Diagnostic Observation Schedule (ADOS), combined with the ADI-R.	Residential proximity (within 1.5 km) to agricultural pesticides it was compared with binary (1 = exposed vs 0 = not exposed) indicators during pregnancy and his association with ASD. Organophosphate pesticides: aOR = 2.07 (95% CI = 1.23–3.50). Chlorpyrifos: aOR = 3.31 (95% CI = 1.48–7.42). Pyrethroids: aOR 1.87 (95% CI = 1.02–3.43).	Recruiting strategy: probably low Blinding: probably low Confounding: probably low Exposure assessment: probably low Outcome assessment: low Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: low

(Continued)

Table 5. (Continued)

Author and year	Study population and sample size (N)	Study design	Exposure	Outcome	Results	Risk of bias
Talbott et al. (2015)	Two-hundred and seventeen children with ASD (169 boys and 48 girls) and two different control groups: 226 matched TD children (175 boys and 51 girls) and 4971 controls (3980 boys and 991 girls) generated from a random sample using birth certificates (BC) (Pennsylvania).	Case-control study	Exposure to arsenic, chromium, methylene chloride, styrene, lead, cyanide, PAHs, among others from ambient air pollution concentrations are estimated using modeled data from the 2005 NATA data.	ASD self-reported by family is diagnosed according to specific tests either such as ADOS or the Social Communication Questionnaire (SCQ).	Comparing fourth to first quartile of exposures: Styrene: aOR = 1.61 (95% CI = 1.08–2.38). Chromium: aOR = 1.60 (95% CI = 1.08–2.38). Methylene chloride: aOR = 1.41 (95% CI = 0.96–2.07). PAHs: aOR = 1.44 (95% CI = 0.98–2.11). Remaining compounds were not statistically significant.	Recruiting strategy: probably low Blinding: probably low Confounding: probably high Exposure assessment: probably high Outcome assessment: probably high Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: low
Volk et al. (2011)	Three hundred and four children with ASD (263 boys and 41 girls) and 259 TD children (211 boys and 48 girls) (California).	Observational case-control study based on the CHARGE study	Residential proximity to a freeway during pregnancy as a surrogate for air pollution (traffic-related pollutants).	The diagnosis of ASD was evaluated from both the ADOS and the ADI-R.	Residential proximity (≤ 309 m) was compared to distance to the nearest freeway during the third trimester of pregnancy and was associated with ASD in offspring (aOR = 2.22; 95% CI = 1.16–4.42). No association with living close to other main roads during pregnancy and ASD.	Recruiting strategy: probably low Blinding: probably low Confounding: probably high Exposure assessment: probably high Outcome assessment: low Incomplete outcome data: probably low Selective outcome reporting: probably low Conflict of interest: probably low Other bias: low
Von Ehrenstein et al. (2014)	Cohort of children ($n = 148,722$; 75,401 boys and 73,321 girls) of which 768 (624 boys and 144 girls) were diagnosed with ASD (Los Angeles County, California).	Observational cohort study	1,3-butadiene, lead, benzene, toluene, ethyl-benzene, xylenes, formaldehyde, and chlorinated solvents measured by community-based air-monitoring stations in mothers residing at 5 km from air toxics during pregnancy.	ASD cases are identified through records maintained by the California Department of Developmental Services and diagnosed according to the DSM-IV-R.	ASD increased risk per interquartile range increase of exposures: 1,3-butadiene: aOR = 1.59; (95% CI = 1.18–2.15). Meta-para-xylene: aOR = 1.51 (95% CI = 1.26–1.82). Lead: aOR = 1.49 (95% CI = 1.23–1.81). Perchloroethylene: aOR = 1.40 (95% CI = 1.09–1.80). Formaldehyde: aOR = 1.34 (95% CI = 1.17–1.52). ASD risk in the upper quartiles of chemical concentrations compared with those below the median.	Recruiting strategy: probably low Blinding: probably low Confounding: probably high Exposure assessment: probably low Outcome assessment: probably low Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: low
Windham et al. (2006)	Two hundred eighty-four children with ASD (241 boys and 43 girls) and 659 TD children (534 boys and 125 girls), born in 1994 in the San Francisco Bay Area (California).	Observational case-control study	Exposure to 25 environmental pollutants is estimated by the US EPA according to maternal residence at delivery.	The diagnosis of ASD is made by qualified medical professionals according to the criteria of DSM-IV.	Chlorinated solvents: Methylene chloride: aOR = 1.50 (95% CI = 1.06–2.1). Trichloroethylene: aOR = 1.47 (95% CI = 1.03–2.08). Vinyl chloride: aOR = 1.75 (95% CI = 1.25–2.43). Metals: Cadmium: aOR = 1.54 (95% CI = 1.08–2.20). Mercury: aOR = 1.92 (95% CI = 1.36–2.71). Nickel: aOR = 1.46 (95% CI = 1.04–2.06). Other exposures were not associated with ASD.	Recruiting strategy: probably low Blinding: probably low Confounding: probably high Exposure assessment: probably low Outcome assessment: probably low Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: low

TD: typically developing; EPA-NATA: US Environmental Protection Agency National-Scale Air Toxics Assessment; ADI-R: Autism Diagnostic Interview-Revised; OR: odds ratio; aOR: adjusted odds ratio; CI: confidence interval; PAH: polycyclic aromatic hydrocarbon.

Table 6. Studies with the estimation of concentrations of endocrine disrupting chemicals provided by analysis of the concentrations of endocrine disruptors in biological samples.

Author and year	Study population and sample size (N)	Study design	Exposure	Outcome	Results	Risk of bias
Braun et al. (2014)	One hundred seventy-five pregnant women ≥ 18 years from Cincinnati.	Observational study with the prospective birth cohort HOME	Eight phthalate metabolites, BPA, 25 PCBs, 6 organochlorine pesticides, 8 brominated flame retardants, and 4 PFAS in maternal serum or urine samples taken at gestation weeks 16–26.	Mothers completed the SRS questionnaire when children were 4–5 years old to evaluate autistic behavior.	Trans-nonachlor and PBDE-28 were associated with autistic behaviors, $\beta = 4.1$; 95% CI = 0.8–7.3 and $\beta = 2.5$; 95% CI = 0.6–5.6, respectively. No statistical significant associations were observed for PCB-178 ($\beta = -3.0$; 95% CI = -6.3 to 0.2), β -HCH ($\beta = -3.3$; 95% CI = -6.1 to -0.5), PBDE-85 ($\beta = -3.2$; 95% CI = -5.9 to -0.5), and PFOA ($\beta = -2.0$; 95% CI = -4.4 to 0.4).	Recruiting strategy: probably low Blinding: probably low Confounding: probably low Exposure assessment: low Outcome assessment: probably high Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: low
Cheslack-Postava et al. (2013)	Seventy-five children (63 boys and 11 girls) with ASD and 75 matched TD children (Finland).	Nested case-control pilot study in the Finnish Maternity Cohort	It is measured different PCB congeners, PBDE, HCB, DDT, and its metabolite (DDE) in maternal serum samples taken during pregnancy.	ASD in children validated by the ADI-R.	No associations with ASD were found for any compound. The aOR of ASD in the 90th of exposure was compared to the lower end of the control distributions: PCBs: aOR = 1.91 (95% CI = 0.57–6.39). HCB: aOR = 0.89 (95% CI = 0.28–2.76). DDE: aOR = 1.79 (95% CI = 0.51–6.21).	Recruiting strategy: probably low Blinding: probably low Confounding: probably high Exposure assessment: probably low Outcome assessment: probably low Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: low
Liew et al. (2015)	Two hundred and twenty children (187 boys and 33 girls) with ASD and 550 TD children (440 boys and 110 girls) are selected from the Danish National Birth Cohort (Denmark).	Nested case-control study	Six PFASs measured in maternal plasma collected in early or mid-pregnancy.	All diagnoses are based on ICD-10, code F84.0.	No associations were observed for any of the PFASs assessed in relation to ASD. PFOS: RR = 0.92 (95% CI = 0.69–1.22). PFOA: RR = 0.98 (95% CI = 0.73–1.31).	Recruiting strategy: probably low Blinding: probably low Confounding: probably high Exposure assessment: probably low Outcome assessment: probably high Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: low
Lyall et al. (2017)	Five hundred forty-five children with ASD (446 boys and 99 girls) and 418 TD children (345 boys and 73 girls) (California).	Population-based case-control study	Concentrations of 11 PCB congeners and 2 OCPs measured in banked second-trimester serum samples and were compared between both groups.	The diagnosis of ASD based on DSM-IV-TR criteria.	OCPs were not associated with ASD and only 2 PCB congeners showed significant association. Comparing highest with the first quartile of PCBs: the OR of ASD was PCB 138/158: aOR = 1.79 (95% CI = 1.10–2.92) and PCB 153: aOR = 1.82 (95% CI = 1.10–3.02).	Recruiting strategy: probably low Blinding: probably low Confounding: probably low Exposure assessment: low Outcome assessment: probably low Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: low
Miodovnik et al. (2011)	One hundred thirty-seven mothers and their children born at Hospital Mount Sinai (New York City).	Observational prospective cohort study	Concentration of 10 metabolites of phthalates and BPA of maternal urine samples taken during the third trimester of pregnancy.	Mothers completed the SRS for detecting and measuring the severity of autistic behavior.	Σ LMWP: $\beta = 1.53$; 95% CI = 0.25–2.8. MEP: $\beta = 1.38$; 95% CI = 0.23–2.53.	Recruiting strategy: probably low Blinding: probably low Confounding: probably low Exposure assessment: low Outcome assessment: probably high Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: low

(Continued)

Table 6. (Continued)

Author and year	Study population and sample size (N)	Study design	Exposure	Outcome	Results	Risk of bias
Nowack et al. (2015)	Out of 133 invited parents, 100 filled out the questionnaire SRS (N = 100, 54 boys and 46 girls) (Duisburg, Germany).	Observational cohort study	Concentrations of PCDD/Fs and PCBs measured in maternal whole blood samples during pregnancy.	Diagnosis and measurement of autistic behavior by the SRS.	Overall, PCDD/Fs and PCBs were negatively associated with autistic behavior; PCDD/Fs: $\beta = -6.66$ (95% CI = -11.88 to 1.44; $p < 0.05$); PCBs: $\beta = -3.99$ (95% CI = -8.61 to 0.64; $p = 0.09$).	Recruiting strategy: probably low Blinding: probably low Confounding: probably high Exposure assessment: probably low Outcome assessment: probably high Incomplete outcome data: probably low Selective outcome reporting: low Conflict of interest: low Other bias: low

β -HCH: β -hexachlorocyclohexane; DDT: dichlorodiphenyltrichloroethane; DDE: dichlorodiphenyldichloroethylene; BDE: tetrabromodiphenyl ether; HCB: hexachlorobenzene; LMWP: low-molecular weight phthalate; ICD-10: *International Statistical Classification of Diseases and Related Health Problems—Tenth Revision*; MEP: monoethyl phthalate; PFAS: perfluoroalkyl substances; ADI-R: Autism Diagnostic Interview-Revised; PCB: polychlorinated biphenyl; PFOS: perfluorooctane sulfonate; BPA: bisphenol; OCPs: organochlorine pesticides; PCDD/Fs: polychlorinated dibenzo-p-dioxins and dibenzofurans; PBDE: polybrominated diphenyl ether; PFOA: perfluorooctanoate; HOME: Health Outcomes and Measures of the Environment; SRS: Social Responsiveness Scale; RR: risk ratio; CI: confidence interval.

formaldehyde, chlorinated solvents, traffic-related pollutants such as diesel particulate, agricultural pesticides such as organochlorines, organophosphates, carbamates, pyrethroids, organochlorates, and chlorpyrifos as well as polycyclic aromatic hydrocarbons (PAHs), among others. This set of studies is the one that encompasses the widest variety of EDCs with a single study including 25 EDCs (Windham et al., 2006). This can be due in part to the fact that the exposure information comes from data previously collected by different environmental control agencies or programs, and therefore, this information is readily available to use. For this group of studies, the sample sizes are notably larger than in the previous group with the smallest including 217 children with ASD; however, the eschewed male-to-female ratio still appears. All population studied were from the United States. ASD diagnosis was made using DSM-IV criteria in 6/9 studies. In the remaining, Autism Diagnostic Observation Schedule (ADOS) was used in two and ADI-R in one. All the studies found statistically significant associations between prenatal exposure to numerous different EDCs and ASD diagnosis in the offspring.

In the studies where exposure to EDCs is evaluated using biological samples (Braun et al., 2014; Cheslack-Postava et al., 2013; Liew et al., 2015; Lyall et al., 2017; Miodovnik et al., 2011; Nowack et al., 2015), half are case-controls and the other half are prospective cohorts. The EDCs studied include phthalates, BPA, PCBs, organochlorine pesticides (OCPs) including dichlorodiphenyltrichloroethane (DDT) and its metabolite dichlorodiphenyldichloroethylene (DDE), brominated flame retardants (BFRs), perfluoroalkyl substances (PFAS), PBDE, 1,3-butadiene, lead, and chlorinated solvents. Among these studies where exposure measurement was based on laboratory analysis, Braun et al. (2014), Lyall et al. (2017), and Miodovnik et al. (2011) were rated as “low” and Cheslack-Postava et al. (2013), Liew et al. (2015), and Nowack et al. (2015) as “probably low” depending on the specific sample and laboratory technique used as well as the timing of the analysis. Most studies related exposures to dichotomized ASD diagnosis based on DSM or *International Classification of Diseases* (ICD) criteria; however some, those using Autism Treatment Evaluation Checklist (ATEC), Child Behavior Checklist Korean version (K-CBCL), Social Communication Questionnaire (SCQ), Social Responsiveness Scale (SRS), and Childhood Autism Rating Scale (CARS) were also able to analyze behavioral outcomes as dimensional constructs, in some cases linking exposure levels to severity. While in general, this group of studies had noticeably smaller sample sizes than the other two groups of studies reviewed, which is to be expected in studies that use biological samples, Lyall et al. (2017) stands out as it includes a sample of over 500 children with ASD which is more than any of the studies in the first group that used



Figure 2. Summary of risk of bias assessment across individual studies. Review of authors' judgments (low, probably low, probably high, and high risk) of bias for each risk of bias domain for each included study ($n = 25$).

questionnaires/interviews for the collection of data on exposure to EDCs. Half of the studies included populations from the United States and the other half included European populations, specifically from Germany, Finland, and Denmark. The results showed a statistically significant risk of ASD in only one study and for only two specific PCB congeners (Lyall et al., 2017), while the remaining studies found non-statistically significant risk.

Summary of the results of all included studies

As a whole, the exposure to EDCs was associated with an increased risk of ASD in the studies included in this review. The main differences among studies were the sample size (from 30 to around 300,000 patients), the age of children, and the measurement of the EDC exposure. The EDCs that presented statistically significant odds or

Table 7. Overall quality and strength of the human evidence (Woodruff et al., 2011).

Factor	Explanation	
Risk of bias	Downgrades	
	0 to -1	Based on the high/probably high risk of bias across the studies, mostly driven by the exposure assessment methods and the outcome evaluation (DSM, ICD-10, SRS, ADOS, and ADI-R). The lack of specificity across different types of EDCs was of special concern.
Inconsistency	0	With few exceptions (Cheslack-Postava et al., 2013; Liew et al., 2015; McCanlies et al., 2012), results across studies are generally consistent in the magnitude and direction. Although most of the studies showed positive EDC-ASD associations, the magnitude of the effect was small, and the statistical significance was not reached in many of them.
Indirectness	0 to -1	Based on the adequate assessment of the exposure at individual level. There is a lack of individual EDC (or metabolites) and/or the exposures are not directly measured; for instance, Larsson et al. (2009) use the floor material, McConlies et al. (2012) use the occupational exposure, and Volk et al. (2011) use the residential proximity as indicators of EDCs.
Imprecision	0	We judged that the CIs for ASD risk were considered as being excessively large.
Publication bias	0	There was no reason to suspect of publication bias. The search was comprehensive, and the most studies were generally consistent among their findings.
Magnitude of effect	Upgrades	
	0 to +1	Although some of the articles (around 38% of the studies) showed strong associations (aRR/aOR >2) between EDC and ASD, most of the studies (around 58%) found slight associations (RR/OR <2).
Dose-response	0	We found there was some evidence of a dose-response relationship.
Confounding	0	We did not find evidence that possible residual confounding influenced results. In the studies retrieved potential confounders and effect modifiers they were examined including population characteristics such as race and ethnicity distribution, whether the tract was urban or rural, level of education, age of participants, percentage of the population below the poverty line, and median household income, among others.
Quality of evidence	Overall rating	
	Moderate	We judge that the results obtained from the retrieved studies do not change the quality of the initial evidence.
Strength of evidence	Limited	Although there is a positive association trend between prenatal exposure to certain EDCs and the risk of ASD in the offspring, due to the limitations present in the studies available so far, conclusive evidence cannot be extracted.

DSM: *Diagnostic and Statistical Manual of Mental Disorders*; ICD-10: *International Statistical Classification of Diseases and Related Health Problems—Tenth Revision*; SRS: Social Responsiveness Scale; ADOS: Autism Diagnostic Observation Schedule; ADI-R: Autism Diagnostic Interview—Revised; EDCs: endocrine disrupting chemicals; ASD: autism spectrum disorder; CIs: confidence intervals; RR/OR: risk or odds ratio.

risk ratios (OR/RR) of ASD >2 in any of the studies were those classified as “industrial chemical contaminants” (e.g. lacquers, asphalt, styrene, and xylene), “flame retardants” (e.g. PBDE congeners), “exhaustion and combustion products,” “agricultural pesticides” (e.g. pyrethroids, organochlorines, and organophosphates), “plastics” (bisphenol A), PCB congeners, and mercury; “heavy metals” (cadmium, chromium, lead, and nickel), and “phthalates” and reported OR/RR of ASD <2. PFAS and DDT metabolites did not reach the statistical significance (Tables 4 to 6).

Summary of the quality and strength of the evidence

Risk of bias was generally “low” or “probably low” across studies for the majority of domains other than those referring to confounding factors, exposure assessment, and

outcome assessment, with several studies rated as having a “high” or “probably high” risk of bias (Figure 2). While the studies assessing the exposure through questionnaires/interviews were rated as “probably high” risk of bias, those using a surrogate indirect measure of occupational exposure were classified as “high” risk and those using air quality monitoring stations, or historical emissions databases as “probably low.” Based on evaluation using the Navigation Guide criteria, the initial quality of evidence was rated as “moderate,” a rating which was retained after the evaluation of the studies included in this review. The decisions leading to this rating are based primarily on the concern that many of the studies showed “high” or “probably high” exposure assessment risk of bias mainly because of the exposure assessment methodology, which included extrapolation of data from the amount of emissions to individual or community exposures, measuring exposure using varied metrics (i.e. environmental monitoring, emissions-based

modeling, or occupation/work place as exposure estimation). Therefore, the quality of the evidence cannot be upgraded, but the risk of bias is also not strong enough in a significant amount of domains to warrant the downgrading of the quality of the evidence and the initial moderate rating is maintained.

Prenatal exposure to EDCs was reported to be associated with an overall increased risk of ASD. The strength of this evidence is constrained, however, by the scarcity of studies carried out for individual EDCs, together with the generally small sample sizes reported, and the methodological limitations noted previously. Therefore, the strength of the overall body of evidence on a positive association between prenatal EDC exposure and offspring ASD diagnosis was rated as “limited” (Table 7). With more studies and with more adequate methodologies, the observed effect could change, and with it, the conclusions derived in this review.

Discussion

This systematic review aimed to evaluate the quality and strength of the findings in studies assessing exposure to EDCs, compounds with the capacity to disrupt normal neuro-physiological mechanisms and interfere with the endocrine system (Ghosh et al., 2015), during pregnancy and future ASD diagnosis of those children whose mothers were exposed to EDCs. The treatment of possible methodological limitations was considered in order to summarize the evidence available to date and aid in the design of future studies.

Biological plausibility

The available literature regarding the etiologic role of endocrine factors in ASD is limited and inconclusive. Understanding the potentially crucial role of endocrine factors and their effect on various stages and aspects of the neurobiological mechanisms of normal social and behavioral neurodevelopment will facilitate an understanding of the rationale for the search of a possible endocrine etiology in ASD.

There is still much for us to comprehend about the mechanisms by which EDCs disrupt correct neurodevelopment; however, epigenetic mechanisms are usually presented as one of the strongest candidates. Prenatal exposures to EDCs, through specific epigenetic changes, may lead to altered hormonal signaling pathways that ultimately induce a variety of autistic traits (Braun, 2012; Ghosh et al., 2015; Siu & Weksberg, 2017; Skinner et al., 2014). For instance, Testa et al. (2012) report that the fully oxidized form 5-oxo-MEHP measured in urine showed 91.1% specificity in identifying patients with ASDs. However, relatively a few studies have been able to adequately account for phenotypic variability between individuals with ASD, and

therefore, other possible mechanisms of action for EDCs in the etiology of ASD must continue to be explored further.

There are endocrine-related factors that act as chemical messengers, whose targets are brain structures known to be involved in different aspects of social development, which facilitate the acquisition of different cognitive and social behaviors. Therefore, any imbalances in these chemical neurotransmissions could theoretically lead to defective or abnormal cognitive and social behaviors that are the hallmarks of ASDs. EDCs can act through agonistic or antagonistic interactions with hormone receptors and affect multiple endocrine pathways, hormonal and homeostatic systems, altering the synthesis, transport, and metabolism of endogenous hormones (Cao et al., 2013; Ji et al., 2013; Lange et al., 2009; Svehnikov et al., 2014; Yu et al., 2014; Zhao & Hu, 2012). Given that most of the effects of EDCs are exerted through disturbances in estrogen or androgen-mediated processes, EDCs can particularly disrupt steroidogenesis (Del-Mazo et al., 2013; Knez, 2013; Marques-Pinto & Carvalho, 2013; Zhang et al., 2014).

The clear proclivity of ASDs for the male sex, with autism being 4 times more common in males and Asperger's syndrome more than 10 times more common in males, has led to research on the possible role of testosterone levels in the etiology of ASDs. According to a study by Henningsson et al. (2009), variance in androgen receptor gene encoding may predispose females to ASDs. It has been shown that high prenatal exposure to free testosterone can predict development of ASD traits in children (Auyeung et al., 2010). In a study of adult women with ASDs, they were found to have increased incidence of hirsutism, polycystic ovary syndrome, irregular menstrual periods, and severe acne, all of which are typical of a hyperandrogenic state (Ingudomnukul et al., 2007). In that same study, when mothers of children with ASDs were compared with mothers of normal children, there was also some evidence of a hyperandrogenic state (Ingudomnukul et al., 2007). This would suggest that the children with ASDs may have a genetic predisposition to a hyperandrogenic state that may predispose them to ASDs. Although there is evidence of a robust association between testosterone and ASDs (Auyeung et al., 2010; Hönekopp, 2011; Hönekopp et al., 2007; Ingudomnukul et al., 2007; Schulkin, 2007), it is difficult to prove causality. Moreover, the relationship between EDCs and ASD is further muddled by the fact that most of the more common EDCs actually have anti-androgenic properties, and therefore, EDC exposure could potentially offer a protective effect on ASD risk.

Many EDCs are xenoestrogens able to adversely impact estrogen signaling by interacting with two estrogen receptors (ERs): ER α and ER β . While a recent study shows that prenatal estrogen contributes to ASD likelihood (Baron-Cohen et al., 2020) extending the finding of elevated

prenatal steroidogenic activity in ASD (Auyeung et al., 2010; Baron-Cohen et al., 2015; Braun, 2012; Craig et al., 2011), estrogen also facilitates the secretion of oxytocin, which plays a central role in social development (Choleris et al., 2003) and there is some evidence that its systemic administration improves autistic behavior, social information retention, emotion recognition and repetitive behavior (Heinrichs et al., 2009; Hollander et al., 2003, 2007) while low levels were associated with poor performance on a cognitive test battery in children with ASD (Modahl et al., 1998). Therefore, xenoestrogen EDCs could both pose a risk, associated with prenatal estrogen exposure, or be a protective factor, as estrogen aids in the secretion of oxytocin.

EDCs can interfere with thyroid hormone (TH) and thyroid-stimulating hormone (TSH) signaling through various pathways across species by altering deiodinase activity (Meerts et al., 2002; Noyes et al., 2013; Viluksela et al., 2004), inhibiting TH excretion or metabolism (Butt & Stapleton, 2013; Nishimura et al., 2002), blocking iodine uptake by thyroid cells (Tonacchera et al., 2004), competitively binding to the thyroid transport protein transthyretin, inhibiting human thyroid peroxidase (Schmutzler et al., 2004, 2007), and acting as an antagonist of complexes from the thyroid hormone response elements (Hamers et al., 2011; Moriyama et al., 2002). Early life disruptions in the synthesis and secretion of thyroid hormones caused by EDCs have been hypothesized to play a role in ASD etiology given their critical role in neurodevelopmental processes (Andersen et al., 2014; Chevrier et al., 2013; Gillberg et al., 1992; Johns et al., 2015; Khan et al., 2014; Morreale de Escobar, 2001; Morreale De Escobar et al., 2004; Román, 2007; Stamou et al., 2013). TH abnormalities are known causes of mental retardation (Büyükgöbüz, 2006; Pemberton et al., 2005), and evidence suggests abnormal maternal and neonatal TH levels can impact other neurodevelopmental outcomes and structural brain development (Alkemade, 2015; Blackburn, 2009; Freire et al., 2010; Haddow et al., 1999; Morreale de Escobar, 2001; Morreale De Escobar et al., 2004; Rovet, 2014; Williams, 2008). A recent study indicates that while maternal thyroid conditions are associated with increased ASD risk in children, the link may not be due to the direct effects of thyroid hormones (Rotem et al., 2020). Rotem et al. (2020) suggest that factors that are known to influence maternal thyroid function should be examined for possible involvement in ASD etiology.

Challenges in the study of ASD and EDCs

To establish a causal link between two factors, such as prenatal exposure to EDCs and later ASD diagnosis of the offspring, the existence of reliable epidemiological studies with consistent results is normally required. However, human studies focusing on exposure to EDCs have complicated

challenges, which will be detailed in the following sections, that need to be addressed so effect estimates obtained in these analyses may be causally interpreted (Lee, 2018). Epidemiological studies of ASD and EDCs have inherent methodological challenges including, but not limited to, the variability in the process of the differential diagnosis of ASD, the lack of a clear definition for EDC, and deficient guidelines for the best methodology for determining EDC exposure. Another important challenge comes from the difficulty of conducting accurate exposure assessments due to the presence of non-monotonic dose-responses (NMDRs), the non-existence of adequate control groups, timing, issues concerning mixtures, the complexity of the kinetics and metabolism processes involved, the effects of mediating and modulating factors, and the other possible unknown effects of confounding factors (Lee, 2018). This complexity must be taken into account when reviewing the information available from human epidemiological studies on EDCs (Lee & Jacobs, 2015). Knowing and understanding these methodological challenges are essential in order to correctly interpret the results of the currently available studies and to properly design future studies minimizing as much as possible the effects of these challenges (Lee & Jacobs, 2015).

Differential diagnosis of ASD. There is burgeoning research on how to improve the prognosis of individuals with ASD; however, the field is held back by the multiplicity of ways of reaching the differential diagnosis of ASD (Matson, 2007). The use of numerous different diagnostic systems (ICD-10, ICD-11, DSM-IV, DSM-IV-TR, or DSM-V) and assessment tools (ATEC, ADOS, ADI-R, M-CHAT, or SCQ, among others) in the diagnosis of ASD poses a methodological challenge on the study of the available literature relating to ASD, and until a universally accepted gold standard is established for ASD diagnosis, this challenge will remain a part of these studies. However, DSM-IV and V are a well-accepted criterion for ASD diagnosis and the different diagnostic systems and assessment tools in use to assess DSM domains have relatively high concordance between them. Rather than focusing on the use of different diagnostic systems, the focus should perhaps be more specifically geared at differentiation between ASD subtypes and ASD diagnosis and traits.

Definition of EDCs. Currently, there is no consensus on what constitutes an EDC (Chang et al., 2009) and precise definitions are important when dealing with risk assessment (Christensen et al., 2003). Although this disagreement over the definition of EDC makes the study of EDCs more difficult, efforts are underway to establish a definition that is scientifically accurate as well as useful from a regulatory standpoint (European Food Safety Authority (EFSA) Scientific Committee, 2013; USEPA, 2019; Zoeller et al., 2012). Hundreds of chemicals have been given the EDC label, but the vast majority have not been

thoroughly tested if at all, and therefore, the catalog of information needed to run accurate assessments is incomplete (UNEP & WHO, 2013).

Assessment of exposure to EDCs. There are still many uncertainties and unknowns in regard to EDCs and the best methodology to determine a person's exposure remains unclear (Beausoleil et al., 2013). While some decision-making organizations, such as government agencies in Australia (Environmental Health Standing Committee (enHealth), 2002; Natural Resource Management Ministerial Council et al., 2008), the EU (Beronius et al., 2009; Bodar et al., 2002; European Commission Joint Research Center et al., 2003), and the USEPA (2002) have attempted to provide guidelines to evaluate the potential risk of EDCs, under the existing regulations, EDCs are not addressed comprehensively (Chang et al., 2009; Hecker & Hollert, 2011).

The accurate assessment of exposure is key to obtaining valid effect estimates or measures of association and the measurement error of the exposure variable can substantially impact the estimation of the association between said exposure variable and the studied outcome (Lee & Jacobs, 2015). The patterns of exposure to many EDCs differ from that of traditional contaminants and further complicate their exposure profile (Greene et al., 2012). Due to their ubiquitous presence (Kolpin et al., 2002; Snyder & Benotti, 2010), long-term, low-dose, sub-chronic, and chronic exposures are common (UNEP & WHO, 2013). The assessment of exposure to EDCs by questionnaires is unreliable and internal dose markers or proxies are considered much more effective (Lee & Jacobs, 2015; Weisskopf & Webster, 2017). EDC exposure is life-stage and timing dependent (Vandenberg et al., 2013), and there are cases in which timing of the dose is more important than the magnitude (Gee, 2008; Martin et al., 2007) without forgetting that some EDCs can be active at extremely low doses, and for some EDCs, there may not be a safe thresholds (Campbell et al., 2006; Cooney, 2000; Hecker & Hollert, 2011; Kortenkamp, 2008; Vandenberg et al., 2013; Welshons et al., 2006). The effects of prenatal or early life EDC exposure may manifest later on in life or even in future generations due to the persistence and susceptibility to undergo bioaccumulation of some EDCs (Ahel et al., 1993; Anway et al., 2005; Dietert, 2014; Grealley & Jacobs, 2013; Hooper et al., 1990; Hu et al., 2005; Kutz et al., 1991; Liu et al., 2012; Liebig et al., 2005; Manikkam et al., 2012; Norstrom et al., 1978; Thomas & Colborn, 1992; Wolstenholme et al., 2012). The long lag period between exposure and outcome manifestation makes it more difficult to link exposures and effects (Manikkam et al., 2012; Weber et al., 2006) which can be seen in the fact that it has taken years for the health implications of EDCs to be recognized (Anway & Skinner, 2008; Newbold et al., 2006). However, some EDCs do not actually bioaccumulate and

their half-life can in fact be quite short; common short half-life EDCs include BPA, phthalate, or PAHs (Dominguez-Romero & Scheringer, 2019; Gendre et al., 2004; Li et al., 2012; Motorykin et al., 2015; Thayer et al., 2015). This brings with it its own complications in the exposure assessment task (e.g. for some, it is unclear whether a single spot urine test during gestation could provide an accurate estimate of exposure throughout gestation due to high intra-person variability of samples across time).

While human biological monitoring of exposure has many advantages compared with environmental monitoring, the complexity of analyzing human biological matrices must also be considered. For many EDCs, there are multiple potential biological matrices that may be used to assess prenatal exposure such as maternal blood, cord blood, urine, and hair that present different analytical challenges, such as sample contamination, dilution, volume expansion, biases arising from compliance with biospecimens collection, and the influence of body composition, among others that should be considered when choosing a biological matrix to analyze. Sample collection must also be performed in a time as to capture the etiologically relevant window of exposure specially for non-persistent EDCs, whereas for persistent EDCs, timing of sample collection may be more flexible. Collecting samples from multiple matrices and at different times of exposure may be advantageous since allows for comparison of levels across matrices and exposure windows.

Environmental exposure to EDCs usually involves exposure to mixtures (EFSA, 2010; Natural Resource Management Ministerial Council et al., 2008). The combination effects that appear when EDCs interact with each other or with other compounds can be additive, synergistic, or attenuative (Huang et al., 2007; Kortenkamp, 2008; Kortenkamp et al., 2009), and only a better understanding of real-life exposures can determine the real risk posed by exposure to mixtures (Kortenkamp et al., 2009).

Given the omnipresence of EDCs, finding unexposed control groups is an important methodological problem without a simple practical solution. NMDRs seem to appear often when studying the effects of EDCs (Beausoleil et al., 2013; Lagarde et al., 2015). The absence of a truly unexposed control group affects the estimation of effect or measure of association in the presence of a NMDR, and the likelihood of underestimating the effect or association increases when there is no threshold dose below which no effects are observed, as the mean exposure levels of the control group are higher (Lee & Jacobs, 2015).

Mechanisms of action of EDCs. EDCs can have very complex multi-component modes of action that manifest uniquely within a specific species (Eertmans et al., 2003; EFSA, 2010; Welshons et al., 2006). This complexity makes it difficult to adequately extrapolate information

and extracting direct links would be an oversimplification and results must be interpreted with caution (EFSA, 2010; Guzik & Swan, 2006). Even in the cases where the modes of action, mechanisms, and extrapolation are relatively well-established, EDCs can display characteristics that do not conform to the established traditional frameworks (Fuhrman et al., 2015).

Effects of EDCs. Another unresolved issue is the selection of what toxicological data should be used to determine the risk derived from EDC exposure (Vandenberg, 2012). This comes down to the selection of the adverse effect for which there is no “gold standard,” and therefore, the most sensitive adverse endpoint is usually chosen (Soto et al., 1995).

The effects on health and development currently attributed to EDCs are often multi-factorial and adjusting for potential confounders is key in order to reduce the risk of bias in the estimation of relative risk ratios (Lee & Jacobs, 2015). However, correct adjustment for confounders is a concept difficultly carried out especially as exposure to EDCs is closely associated with many established risk factors (Lee & Jacobs, 2015).

Challenge summary. In order to accurately interpret the results from studies involving EDCs and ASD, the limitations imposed by the methodological challenges and the gaps in knowledge affecting the study must be understood and taken into consideration. A study riddled with potential inaccuracies will not stand on its own as reliable evidence; however, if the inaccuracies and/or unknowns are consistent, the study results can serve as a basis of comparison with other studies with the same inaccuracies and/or unknowns.

Because of differences between environmental and clinical health sciences related to the aforementioned methodological limitations as well as evidence base and decision context, systematic review methodologies used in the clinical sciences were not seamlessly applicable to environmental exposures (Woodruff et al., 2011). The Navigation Guide methodology, which is a systematic, robust, and rigorous approach specific for the evaluation of the evidence-based environmental health, was therefore used. To date, the Navigation Guide method has been used in a few studies (Johnson et al., 2014, 2016; Koustas et al., 2014; Lam et al., 2015, 2016; Vesterinen et al., 2015).

Main limitations of the review process

This review process presents some limitations. First, the review itself may be sensitive to publication bias, and it might not have retrieved all the relevant publications on the subject (e.g. studies that could have had repercussion in the conclusion of this review). Second, the scarce number of studies on the subject and the wide variety of different EDCs were addressed. Currently, the available

literature on exposure to a specific EDC during pregnancy and its association with ASD is limited. While there are some studies that research the effects of individual EDCs or families, not enough information is available to carry out a review such as the one done in this work. The only EDC studied more extensively individually that the authors are aware of is mercury, meanwhile, other EDCs are usually studied as part of larger groups such as “solvents,” “volatile organic compounds,” or “pesticides” which are not clearly defined and may contain compounds with very different mechanisms of action. Third, it was not possible to explore the influence of the period of EDCs exposure during pregnancy, given that most of the studies did not consider times of exposure (first, second, or third trimester of pregnancy).

Importantly, in order to faithfully apply all the steps contemplated in the methodology of the Navigation Guide, the quality ratings of animal evidence should be also conducted and integrated with the quality of the overall body of human evidence. This is a preliminary review carried out to inform a larger project that will include a systematic review of the current experimental and animal evidence on suggested relationships between the EDCs and autistic behavior. (Causality may be difficult to impute, and in any event, the behavior is an analog to autistic behavior in human subjects.). The end result will be one of five possible statements about the overall strength of the evidence: “known to be toxic,” “probably toxic,” “possibly toxic,” “not classifiable,” or “probably not toxic” (Woodruff et al., 2011; Woodruff & Sutton, 2014).

Conclusion

This description of studies published to date aimed to serve as a summary of the current available scientific evidence and its quality. In general, the studies found that those mothers with children diagnosed with ASD were more exposed to EDC during pregnancy. Nevertheless, the overall quality and strength of the available studies were “moderate” and “limited,” respectively, due to the methodological limitations regarding the inclusion of potential confounding factors and the lack of accuracy of exposure assessment methods in the studies. As previously stated, the Navigation Guide is a systematic and transparent method of research synthesis in environmental health as was developed with the goal of expediting evidence-based recommendations for preventing harmful environmental exposures, and therefore bridging the gap between clinical and environmental health sciences. When the gap that is trying to be bridged is that between ASD and EDCs, the methodological challenges must be recognized as accounting for all possible biases is almost impossible even if studies are conducted with the highest scientific rigor. This limitation would be common to most studies on the association

between ASD and EDCs, and therefore, it might be more advisable to use a comparative rather than absolute ranking system when evaluating the strength and quality of the evidence available.

The ubiquitous presence of EDCs worldwide, their persistence and bioaccumulation, and the biologically plausibility on the associations between EDCs exposure during pregnancy and later ASD in childhood highlight the need to carry out well-designed epidemiological studies. While all EDCs have in common that they are compounds with the capacity to disrupt normal neuro-physiological mechanisms and interfere with the endocrine system, the underlying biological mechanisms involved are different and further studies on specific EDCs or families are needed. Future studies should aim to overcome the methodological limitations observed in the currently available literature in order to be able to better inform public policy to prevent exposure to these potentially harmful environmental chemicals.

Author contributions

S.M.-B. and M.M.S.-V. conceived the review. S.M.-B., C.D.-V., and M.M.S.-V. performed the literature search, collected the data, wrote the first draft, and edited subsequent drafts. A.L.-G., A.M.-S., I.P.-C., and J.L.-M. supervised data collection and contributed significantly to editing the manuscript. S.M.-B., C.D.-V., and M.M.S.-V. reviewed the data collected and contributed significantly to editing the manuscript. All authors approved the final version of the manuscript.

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Supplemental material

Supplemental material for this article is available online.

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