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Association Between Exposure to Pesticides and ADHD or Autism Spectrum Disorder: A Systematic Review of the Literature

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Abstract

Objective: To conduct a systematic review of studies assessing the relationship between exposure to pesticides and ADHD or Autism Spectrum Disorder (ASD).

Methods: Based on a pre-registered protocol in PROPSERO (CRD42018107847), we searched PubMed, Ovid databases, and ISI Web of Knowledge with no date/language/document type restrictions, up to May 2019. The Newcastle Ottawa Scale was used to assess study quality.

Results: Among the 29 retained studies, 13 focused on ADHD, 14 on ASD, and two on both disorders. Ten studies reported a significant association between exposure to pesticides and ADHD/ADHD symptoms and 12 studies found a significant association with ASD/ASD traits. The strengths of the association and the possible confounders controlled for varied substantially across studies.

Conclusion: Whilst there is some evidence suggesting a possible link between pesticides and ADHD/ASD, heterogeneity across studies prevents firm conclusions. We provide methodological indications for future studies. *(J. of Att. Dis. XXXX; XX(X) XX-XX)*

Keywords

ADHD, pesticides, systematic review

Introduction

ADHD, defined by developmentally inappropriate, pervasive, and impairing levels of inattention and/or hyperactivity/impulsivity, is one of the most common neurodevelopmental disorders in childhood (Cortese & Coghill, 2018). The treatment of ADHD, which includes pharmacological (Cortese et al. 2018) and non-pharmacological (Sonuga-Barke et al., 2013) strategies, is mostly symptomatic, rather than curative. Autism spectrum disorder (ASD), defined by qualitative alterations in communication/interaction associated with restricted interests and repetitive behaviors, is another common neurodevelopmental disorder in childhood, with no available curative treatment (Lord et al., 2018). Advancing our understanding on the etiology and pathophysiology of ADHD and ASD may lead to more effective treatments in the long term.

The etiology of ADHD and ASD is thought to reflect a complex interplay between genetic and environmental factors (Abrahams & Geschwind, 2008, Archer et al., 2011). Among the environmental risk factors, over the past years there has been an increasing interest on the possible role of pesticides. This body of research is based on mounting evidence showing the neurotoxicity of pesticides on the central nervous system. Indeed, exposure to chemicals may adversely affect the development of infants and children through various toxicological pathways. Organophosphates (OPs) have been shown to inhibit acetylcholinesterase and disrupt cholinergic signaling (Slotkin, 2004). At doses lower

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than those needed to inhibit acetylcholinesterase, certain OPs affect different neurochemical targets, including growth factors, several neurotransmitter systems, and second messenger systems (Slotkin & Seidler, 2007; Verma et al., 2009). In animal models, changes in the nervous system development as well as sensory, motor and cognitive cerebral functions of rodents have been related to prenatal and early postnatal exposure to chlorpyrifos (Maurissen et al., 2000; Rice & Barone, 2000). Studies in humans have also demonstrated the effect of exposure to organochlorine pesticides on psychomotor development (Torres-Sanchez et al., 2007) and cognitive functions (Ribas-Fito et al., 2003). More specifically, it has been shown that developmental exposure to OPs might have persistent effects on multiple neural systems that may cause ADHD-related traits, such as inattention and cognitive deficits (Heath & Picciotto, 2009; Slotkin, 2004). Additionally, several animal studies have provided evidence that prenatal exposure to pesticides can not only interfere with motor development (De Felice et al., 2015) but also lead to autism-like behavioral abnormalities (Laugeray et al., 2014; Mullen et al., 2012).

Therefore, gaining insight into the possible effects of pesticides on the etiology of ADHD and ASD may have important implications from a scientific as well as a clinical/public health standpoint. To date this body of research has not been systematically appraised. To fill this gap, we conducted a systematic review of studies assessing the relationship between mothers' exposure to pesticides during pregnancy, or exposure of children in early life, and children's ADHD or ASD. The focus on both ADHD and ASD in the same review is relevant considering that the Diagnostic and Statistical Manual of Mental Disorders (5th ed.) (American Psychiatric Association, 2013) removed the veto to co-diagnose these two conditions, so that a dual diagnosis of ADHD and ASD is now common practice in child and adolescent mental health/pediatric/psychiatric services. Indeed, a number of previous reviews (e.g., de Castro Pavia et al., 2019; Martin et al., 2019) in the field of developmental psychopathology have focused on both ADHD and ASD.

Whilst we are aware of previous systematic reviews on one neurodevelopmental condition only, (e.g., ASD in Rossignol et al. [2014], or Lam et al. [2016]), of narrative reviews on the role of pesticides in ADHD and ASD (e.g., [Roberts et al., 2019]) and of another narrative review on pesticides in ADHD (Polańska et al., 2013), to our knowledge, no previous systematic review has explored the role of pesticides in ADHD as well as ASD. While previous systematic reviews focused on one or two types of pesticide only, such as Cimino et al. (2017), we aimed to conduct a large-scale review on a broad range of pesticides.

The aim of the systematic review was to assess to which extent current studies point to significant association between pesticides exposure and ADHD and/or ASD, and to assess the strength of the association reported in each retained study.

Methods

Methods for this systematic review were developed according to the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Liberati et al., 2009). The pre-registered protocol of this study is available in PROSPERO (CRD42018107847).

We searched the following electronic databases with no restrictions in terms of date/language or type of document, from inception up to May 3, 2019: PubMed, Ovid databases (Medline, PsycINFO, Embase + Embase classic), and ISI Web of Knowledge (Web of Science [Science Citation Index Expanded], Biological Abstracts, Biosis, Food Science, and Technology Abstracts). The search terms and syntax for the search in PubMed were as follows: (ADHD [tiab] OR Hyperkinetic disorder [tiab] OR attention deficit [tiab] OR attention-deficit/hyperactivity disorder [tiab] OR attention-deficit hyperactivity disorder [tiab] OR attention deficit/hyperactivity disorder [tiab] OR attention deficit disorder with hyperactivity [tiab] OR hyperkinetic syndrome [tiab] OR hyperkinetic disorder [tiab] OR Autis* [tiab] OR neurodevelopmental disorder* [tiab] OR Asperger* [tiab]) AND (pesticide* [tiab] or defoliant* [tiab] or insecticide* [tiab] or paraquat* [tiab] or fungicide* [tiab] or ddt* [tiab] or weedkiller* [tiab]). We note here that [tiab] means that the term is searched in the title or abstract of the reference. The search terms and syntax were adapted for each of the other electronic databases.

Studies of any design were eligible if they assessed exposure to any kind of pesticides or defoliants or insecticides or paraquats or fungicides or ddt or weedkiller in biological specimens from children/adolescents with ADHD or ASD or in their immediate environment. We included studies that used a formal diagnosis of ADHD/ASD, as well as studies in which the diagnosis of these two disorders was self-reported or studies that evaluated traits of ADHD and ASD via validated questionnaires.

References identified with electronic and manual searches were listed with citation, titles and abstracts in Endnote, Clarivate®; duplicates were removed using the Endnote function "remove duplicates" (Endnote version EndNote X9. Philadelphia, PA: Clarivate Analytics; 2013). The eligibility process was conducted in two separate stages:

1. Two authors independently screened title and abstract of all non-duplicated papers and excluded those not pertinent. A final list was agreed with discrepancies resolved by consensus between the two authors. When consensus was not reached, a third, senior author acted as arbitrator. If any doubt about inclusion exists, the article proceeded to the next stage;
2. The full-text version of the articles passing stage 1 screening was downloaded and assessed for eligibility by two authors, independently. Discrepancies

were resolved by consensus between the two authors and, if needed, a third senior author acted as arbitrator. Two researchers performed independently the data extraction.

The Newcastle Ottawa Scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) was used to assess the quality of the studies included in the systematic review, in relation to the following items, when applicable: A) for case-control studies: 1) Is the case definition adequate?; 2) Representativeness of the cases; 3) Selection of controls; 4) Definition of controls; 5) Comparability of cases and controls on the basis of the design or analysis; 6) Ascertainment of Exposure; 7) Same method of ascertainment for cases and controls; 8) Non-response rate. B) For cohort studies: 1) Representativeness of the exposed cohort; 2) Selection of the non-exposed cohort; 3) Ascertainment of exposure; 4) Demonstration that outcome of interest was not present at start of study; 5) Comparability of cohorts on the basis of the design or analysis; 6) Assessment of outcome; 7) Was follow-up long enough for outcomes to occur; 8) Adequacy of follow-up of cohorts.

Results

From a pool of 800 potentially relevant citations, 29 studies were retained in the systematic review, including 13 focusing on ADHD, 14 on ASD, and two on both ASD and ADHD. Figure 1 reports the PRISMA flowchart. Among the included studies, 10 reported a significant association between exposure to pesticides (OPs, Pyrethroid pesticide, Organochlorine pesticides, polychlorinated biphenyls (PCB)) and ADHD/ADHD symptoms (Table 1) and 12 studies reported a significant association between exposure to pesticides (OPs, Pyrethroid pesticides, Organochlorine pesticides/ PCB, Avermectin, and Imidacloprid) and ASD or ASD-related traits (Table 2).

The results of the NOS assessment are reported in Table 3 (case-control studies) and Table 4 (cohort studies). "Non-response rate" for case-control studies and "Adequacy of follow up of cohorts" for cohort studies were the most critical items, being rated at risk in 100% and 95% of the included case-control and cohort studies, respectively.

In the following sections, we summarize the results from the included studies.

ADHD

Organophosphates (OPs). A number of studies support a significant association between high levels of organophosphates (OPs), or at least some types of OPs, and ADHD/ADHD symptoms, but findings are not consistent across studies and we also found negative studies. Concerning cross-sectional investigations, the study by Yu et al. (2016) in 97 children with ADHD and 110 controls, supported a significant relation between ADHD symptoms and one of the six urinary dialkylphosphate (DAP) metabolites that result from the degradation of different OP, with children with ADHD having significantly higher concentrations of dimethylphosphate (DMP) compared to controls (322.92 ± 315.68 vs. 224.37 ± 156.58 nmol/g adjusted for creatinine, $p < .01$). The relationship between ADHD and DMP levels remained significant even after controlling for a number of sociodemographic and clinical covariates (see Table 1) (adjusted odds ratio: 2.91 [95% CI = 1.13–7.46] when considering DPM concentration > 75th percentile).

In another study of 1,139 children, including 119 with ADHD, Bouchard et al. (2010) found a significant association between ADHD and urinary levels of DAP, including 3 Dimethyl Alkylphosphate molecules (DMAP) (dimethylphosphate, dimethylthiophosphate, dimethyldithiophosphate) and 3 Diethyl Alkylphosphate molecules (DEAP) (diethylphosphate, diethylthiophosphate, diethyldithiophosphate). Adjustment for covariates (gender, age, race/ethnicity, poverty/income ratio, fasting duration, and urinary creatinine concentration) decreased the strength of the association, and made it in general not significant (for a 10-fold increase in total DAP concentration, unadjusted OR = 1.31 [95% CI = 1.06–1.63]; adjusted OR = 1.21 [95% CI = 0.97–1.51]). However, for DMAP metabolites, the association was still significant after adjustment (OR = 1.55 [95% CI = 1.14–2.10]). Additionally, children with concentrations above the median of DMAP had twice the odds of ADHD (adjusted OR = 1.93 [95% CI = 1.23–3.02]). Gender and age did not significantly moderate the results. By contrast, Oulhote and Bouchard (2013) did not observe any significant association between urinary DAP metabolites levels and behavioral scores on the Strength and Difficulties Scale (SDQ) (total score and dimension scales, including hyperactive/inattention) in their sample of 1030 children. Of note, the SDQ provides a general assessment of mental health status, and the dimension scales might not be sufficiently sensitive to specific behavioral ADHD-related problems.

Moving beyond cross-sectional associations, in the study by Marks, Harley et al. (2010) prenatal DAP metabolites in 329 children aged 5 as well those in their mothers during pregnancy were significantly associated with attention problems and ADHD scores on the Child Behavior Check List, CBCL (attention problems: β = .7 points; 95% CI = 0.2–1.2; ADHD: β = 1.3; 95% CI = 0.4–2.1), whilst no significant correlation was found with attention problems at the age of 3.5 y. The levels of those metabolites were also significantly associated with the scores on the K-CPT (Conners' Kiddie Continuous Performance Test), ADHD Confidence Index > 70th percentile (OR = 5.1; 95% CI = 1.7–15.7) and with a composite ADHD measure (OR = 3.5; 95% CI = 1.1–10.7). In this study, for each

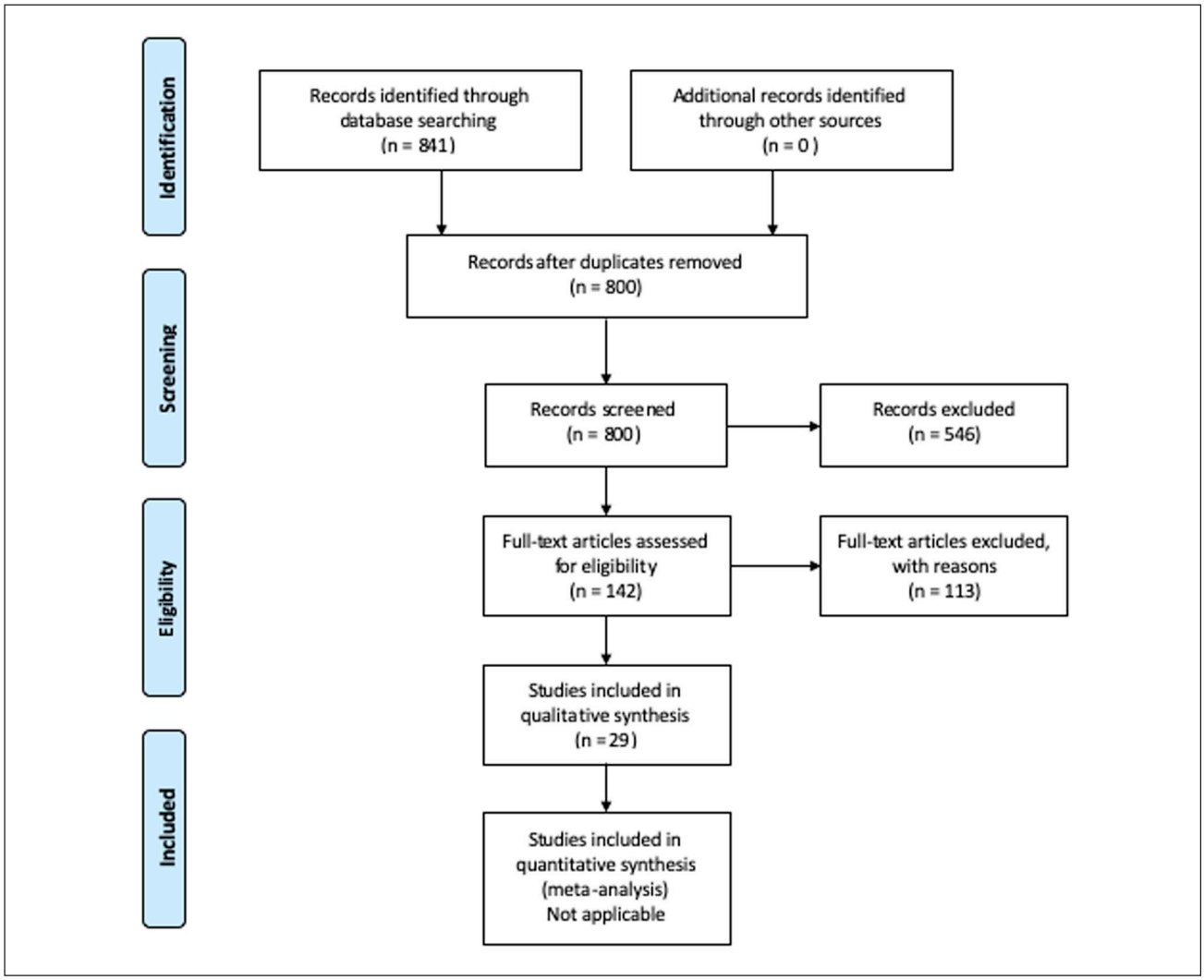

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart.

10-fold increase in DAP urine concentrations, children had five times the odds of scoring > 70% on the ADHD Confidence Index (OR = 5.1; 95% CI = 1.7–15.7). Birth weight, gestational age, breast-feeding, and lead did not significantly confound the associations between DAPs and attention.

By contrast, Eskenazi et al. (2007) did not find any significant association between prenatal or childhood DAPs (evaluated through maternal and child samples of urine serum levels of metabolites) or other OPs (malathion and chlorpyrifos, TCPy) and attention problems on the CBCL at 24 months in 396 children tested at 6, 12, and 24 months, even though the follow-up in this study was at an earlier age compared to the study by Marks et al. (2010).

Three studies focused specifically on chlorpyrifos (via its metabolite 3,5,6-trichloro-2-pyridinol, TCPy). In the study by van Wendel de Joode, Mora et al. (2016) in 140 children (age range: 6.5–9.3 years), chlorpyrifos levels measured in urine were significantly associated with parent-reported cognitive problems/inattention, even after controlling for a number of possible confounders, (aOR = 5.8; 95% CI = 1.6, 22.9) and ADHD Index (aOR = 6.8; 95% CI = 1.8, 28.6) when using the 75th percentile as cut-off points on the Conner's Parent Rating Scale-Revised Short Version (CPRS-R). Another study, (Rauh, 2006) found that at 3 years of age, children (n = 254) who were exposed prenatally (via maternal blood sample) to high levels of chlorpyrifos were significantly more likely to score in the CBCL clinical range for attention problems (Attention Problems: OR = 11.26; 95% CI = 1.79–70.99; ADHD Problems: 6.50, 1.09–38.69) in a logistic regression model including socio-demographic covariates. However, in a sample of 187 mother-child pairs, Fortenberry et al. (2014) did not observe any statistically significant associations between prenatal

Table 1a. Studies on ADHD and Organophosphate (studies listed by alphabetical order of first author's name).

First author and year	Design	Diagnostic/assessment method	Type of biological sample	Type of pesticide	Population	Confounding factors controlled for	Key findings
Bouchard (2010)	Cross- sectional	DISC-IV	Child urinary samples	DAP metabolites: Three DMAP (DMP, DMTP, DMDTP) Three DEAP (DEP, DETP, DEDTP)	1,139 children (8–15 years) including 119 with ADHD	Sex, age, race/ethnicity, poverty/income ratio, fasting duration, and urinary creatinine concentration	Significant association in unadjusted but not adjusted analyses between DAP and ADHD (for a 10-fold increase in total DAP concentration, unadjusted OR = 1.31 95% CI = 1.06–1.63; adjusted OR, (95% CI = 1.21, 0.97–1.51). For DMAP, significant association even after adjustment (OR = 1.5, 95% CI = 1.14–2.10) DEAP not significantly associated with ADHD, n
Eskenazi (2007)	Longitudinal birth cohort	CBCL	Mother and child urinary samples Serum levels from prenatal blood samples	Urinary DAP metabolites: Three DMAP molecules (DMP,DMTP,DMDTP) and three DEAP molecules (DEP, DETP, DEDTP) Malathion Chlorpyrios	396 children Tested at 6, 12, and 24 months, including 356 cases of ADHD	Sex, exact age at assessment, breast-feeding duration, HOME score, household income above poverty threshold, parity, maternal scholastic abilities (tested with PPVT), and maternal depression	Neither prenatal nor child DAPs were associated with CBCL attention problems, MDA and TCPy levels were not associated with any outcome
Fortenberry (2014)	Prospective cohort	CPRS-R, BASC-PRS, CPT	Third trimester mother urinary samples	TCPy (metabolite of chlorpyrifos and chlorpyrifos-methyl)	Mother-child pairs 187 Tested at 7.5 years 181 cases of ADHD	Maternal IQ, maternal education, socioeconomic status, specific gravity, season, breastfeeding, maternal blood lead, child age at testing, child sex, birth length, and head circumference at birth	No significant association between prenatal exposure (third semester) to chlorpyrifos and and chlorpyrifos-methyl (estimated via TCPY) and ADHD symptoms in children
Marks (2010)	Cohort	CBCL NEPSY-II K-CPT HBRS	Mother and child urinary samples	DAP metabolites three DMAP (DMP, DMTP, DMDT) and three DEAP (DEP, DETP, DEDTP)	329 children Tested at 3.5 years, 5 years	Age at assessment, sex, maternal education, depressive symptoms, PPVT score, ≥ 15 hour out-of-home child care/week, breast feeding duration, child care, and breast-feeding, maternal age, parity, marital status, active/passive smoking exposure and regular alcohol use during pregnancy, presence of father in home, maternal work status, and household income at the time of assessment	At age 3.5, prenatal DAP concentrations positively but not significantly associated with attention problems At age 5, prenatal DAPs significantly associated with CBCL attention problems: (β = .7 (95% CI = 0.2,1.2), and ADHD score (β = 1.3; 95% CI = 0.4–2.1, K-CPT ADHD Confidence Index > 70th percentile (odds ratio [OR] = 5.1; 95% CI = 1.7–15.7) and with a composite ADHD indicator of the various measures (OR = 3.5; 95% CI = 1.1–10.7)

(continued)

Table 1a. (continued)

First author and year	Design	Diagnostic/assessment method	Type of biological sample	Type of pesticide	Population	Confounding factors controlled for	Key findings
Oulhote (2013)	Cohort	SDQ	Child urinary samples	DAP metabolites three DMAP (DMP, DMTP, DMDT) and three DEAP (DEP, DETP, DEDTP)	1,030 children 6, 11 years	Sex, age, race/ethnicity, income, parental education, blood lead levels, maternal smoking during pregnancy, birth weight, and urinary creatinine	No significant association between DAP metabolites in urine and scores of hyperactivity/inattention on the SDQ
Rauh (2006)	Prospective Cohort	CBCL	Mother blood samples collected within 2 days after delivery	Chlorpyrifos	228 children Tested at 12, 24, 36 months	Prenatal environmental tobacco smoke exposure (ETS), gender, ethnicity, gestational age at birth, quality of the home care-taking environment, maternal educational level (high school degree versus no high school degree), and maternal IQ	Children prenatally exposed to chlorpyrifos (urine sample collected at delivery at delivery) significantly more likely to score in the clinical range for attention problems and ADHD problems at age 3 years (Attention Problems OR = 11.26 [95% CI = 1.79,70.99] ADHD Problems OR = 6.50, 95% CI = 1.09, 38.69) (regression logistic model including the study covariates)
Van Wendel de Joode (2016)	Cross sectional cohort	CPRS	Child urinary samples	Chlorpyrifo (TCPy)	140 children 6.5 to 9.3 years	Child sex and age at assessment, maternal education, Having repeated a school year, number of siblings, child Body Mass Index (BMI), visual acuity, number of languages spoken at home, creatinine	TCPy concentrations were associated with significantly increased odds (based on the 75th percentile as cut-off points) for parent-reported cognitive problems/inattention (aOR = 1/4 5.8, 95% CI = 1.6, 22.9), oppositional disorders (aOR = 1/4 3.9, 95% CI = 1.0, 16.0), and ADHD Index (aOR = 1/4 6.8, 95% CI = 1.8, 28.6)
Yu (2016)	Case control	Clinical diagnosis supported by SNAP-IV	Child urinary samples	DAP metabolites: three DMAP (DMP, DMTP, DMDT) and three DEAP (DEP, DETP, DEDTP)	97 cases of ADHD 110 controls Mean age 8.9 ± 2.8 years	Gender, maternal and paternal education levels, maternal drinking during pregnancy, and family history of nervous system diseases	Significantly higher urinary concentration of DMP in children with ADHD versus controls (322.92 ± 315.68 vs. 224.37 ± 156.58 nmol/g adjusted for creatinine, $p < .01$).

Table 1b. Studies on ADHD and Organochlorine/Polychlorinated Biphenyls (PCB) (studies listed by alphabetical order of first author's name).

Author	Design	Diagnostic/assessment method	Type of biological sample	Type of pesticide	Population	Confounding factors controlled for	Key findings
Forns (2018)	Cohort	Diagnosis recorded d in population-based registry or via CBCL or SDQ	maternal serum/whole blood, cord serum/plasma or breast milk children age 3, 6, 12, and 24 months	p- p′-DDT and its p- p′-DDE HCB	4437 children 6 to 12 years 266 cases of ADHD	Maternal pre-pregnancy body mass index, maternal age, maternal education, maternal smoking during pregnancy, maternal parity and child's sex	No significant association between p- p′-DDE and HCB exposure and ADHD
Lenters (2019)	Cohort	Nation wide Norwegian Patient Registry	breast milk samples	HCB, β-HCH, oxychlordane p,p′-DDT p,p′-DDE	1199 children 55 cases of ADHD	Child age at linkage, maternal age, and maternal education, parity, smoking during pregnancy, pre-pregnancy body mass index (BMI), marital status, and maternal fatty fish consumption gestational age (SGA) and preterm birth	Breast milk concentrations of β-HCH associated with increased odds of ADHD: (OR = 1.75, 95% CI = 1.22, 2.53), p,p′-DDT associated with lower odds of ADHD (OR = 0.64, 95% CI = 0.42, 0.97).
Sagiv (2010)	Cohort	CRS-T	Cord blood samples	PCB and p,p′-DDE	573 children 7, 11 years	Child age and sex and for maternal age, marital status, smoking during pregnancy, alcohol consumption during pregnancy, local fish consumption during pregnancy, and illicit drug use	Significant association between prenatal PCB and organochlorine in umbilical cord blood or p,p′-DDE and ADHD-symptoms measured with the Conners ADHD Index (Adjusted beta for the association between sum of 4 PCBs and Conners' ADHD index: 0.08, 95% CI = 0.03, 013; adjusted beta for the association between sum of p,p′-DDE and Conners' ADHD index: 0.01, 95% CI = 0.00, 003)
Sioen (2013)	Cohort	SDQ	Cord blood samples	Lead, cadmium, PCBs, dioxin-like compounds, HCB and p,p′-DDE	270 children Mean age of 7.8 ± 0.4 years	Mother's BMI, the age of the mother at pregnancy, weight increase of the mother during pregnancy, smoking during pregnancy, father's BMI of the father, if parents currently smoke, smoking behavior of the maternal grandmother before the birth of the mother, highest education level of both parents, gender of the child and serious infections of the child since birth	Prenatal p,p′-DDE exposure not significantly associated with SDQ hyperactivity score at the age of 7 to 8 years (aOR = 1.736 95% CI = 0.849, 3.550)
Xu (2011)	Cohort	Parental report of ADHD	Child urinary samples	TCPs 2,4,5-TCP and 2,4,6-TCP	2539 children 6 to 15 years 200 cases of ADHD	Age, gender, poverty-to-income ratio, maternal smoking during pregnancy, low birth weight, blood lead and serum cotinine	Compared to children with levels of 2,4,6-TCP below the limit of detection, children with low (<3.58 mg/g) and those with high levels of urinary 2,4,6-TCP (>3.58 mg/g) were significantly more likely to have a diagnosis of ADHD (OR = 1.54 95% CI = 0.97, 2. and OR = 1.77 95% CI = 1.18, 2.66, respectively) Significant association between 2,4,5-TCP, but not 2,4,5-TCP, and ADHD

Table 1c. Studies on ADHD and Pyrethroid (studies listed by alphabetical order of first author's name).

Author	Design	Diagnostic/ assessment method	Type of biological sample	Type of pesticide	Population	Confounding factors controlled for	Key findings
Oulhote (2013)	Cohort	SDQ	Child urinary samples	Five urinary metabolites: 4-F-3-PBA, cis-DBCA, cis-DCCA, trans-DCCA, 3-PBA	1,030 children 6, 11 years	Sex, age, race/ethnicity, income, parental education, blood lead levels, maternal smoking during pregnancy, birth weight, and urinary creatinine metabolite 3-PBA also included BMI and fasting status BMI and fasting status	Pyrethroid metabolite cis-DCCA [3-(2,2-dichlorovinyl)-2,2-dimethylycyclopropane carboxylic acid] significantly associated with total scores of the SDQ (OR = 2.0, 95% CI = 1.1, 3.6) Non significant associations for other Pyrethroid metabolite
Quiros-Alcala (2014)	Cross sectional	Parental report of ADHD	Child urinary samples	Metabolites 3-PBA cis- and trans-DCCA	1861 children 6 to 15 years 148 cases of ADHD	Sex, age, race/ethnicity, household reference education level, low birth weight status, maternal age at child's birth, NICU (neonatal intensive care unit) admission, maternal smoking during pregnancy, day care/preschool attendance, and health insurance, creatinine	Postnatal pyrethroid exposure not significantly associated with parental report ADHD and/or LD
Wagner-Schuman (2015)	Cross sectional	DISC	Child urinary samples	3-PBA	687 children 8 to 15 years 93 cases of ADHD	Child sex, age, race/ethnicity, income, health insurance status, prenatal tobacco exposure, blood lead level (log10-transformed), urinary organophosphate metabolite level (log10-transformed), and urinary creatinine level	3-PBA above the limit of detection. significantly associated with ADHD diagnosis (aOR = 2.42; (95% CI = 1.06–5.57). Hyperactive-impulsive symptoms, but not inattentive symptoms, significantly correlated with 3-PBA

Note. BASC-PRS = Behavioral Assessment Scale for Children; BMI = Body Mass Index; BSID-II = Bayley Scales of Infant Development II; CPRS = Conners' Parental Rating Scales; CBCL = Child Behavior Checklist, ; CPT = Conners' Continuous Performance Test, DISC-IV = Diagnostic Interview Schedule for Children IV; HBRS = Hillside Behavior Rating Scale, HOME = Home Observation for Measurement of the Environment; K-CPT = Conners' Kiddie Continuous Performance Test; NEPSY-II = Developmental Neuoropsychological Assessment; PPVT = Peabody Picture Vocabulary Test; SDQ = Strengths and Difficulties Questionnaire, ; SNAP-IV = Swanson, Nolan, and Pelham, Fourth Revision.

Chemical compounds: cis-DBCA cis-3-(2,2-dibromovinyl)- 2,2-dimethylcyclopropane-1-carboxylic acid, cis-DCCA cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid, DAP dialkylphosphate metabolites, DM dimethyl phosphate metabolites, DMAP Dimethyl Alkylphosphate molecules, DMP dimethylphosphate, DMTP dimethylthiophosphate, DMDTP dimethyldithiophosphate, DEP diethylphosphate, DEAP Diethyl Alkylphosphate molecules, DETP diethylthiophosphate, DEDTP diethyldithiophosphate, HCB hexachlorobenzene, MDA Malathion, p- p′-DDT p- p′- dichlorodiphenyltrichloroethane, p- p′-DDE p-p′-dichlorodiphenyldichloroethylene, HCB hexachlorobenzene, β-HCH β-hexachlorocyclohexane, trans-DCCA trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid, 3-PBA 3-phenoxybenzoic acid, 4-F-3-PBA 4-fluoro-3-phenoxybenzoic acid, TCPs Trichlorophenols, TCPy 3,5,6-trichloro-2-pyridinol.

Table 2a. Studies on ASD and Organophosphates (studies listed by alphabetical order of first author's name).

Author	Design	Diagnostic/ assessment method	Type of biological sample	Type of pesticide	Population	Confounding factors controlled for	Key findings
Eskenazi (2007)	Longitudinal birth cohort	CBCL	Mother and child urinary samples Serum levels prenatal blood samples	Urinary DAP metabolites: Three DMAP molecules (DMP,DMTP,DMDTP) and three DEAP molecules (DEP, DETP, DEDTP)	396 children tested at 6, 12, and 24 months, including 356 cases of ADHD	Sex, exact age at assessment, breast-feeding duration, HOME score, household income above poverty threshold, parity, maternal scholastic abilities tested with PPVT), and maternal depression	Prenatal and postnatal DAPs associated with higher risk of pervasive developmental disorder (Prenatal: aOR = 2.25, 95% CI = 0.99–5.16; Child= aOR = 1.71, 95% CI = 1.02–2.87)
Furlong (2014)	Cohort	SRS	Mother urinary samples collected between 25 and 40 weeks' gestation	DAP (including DEP and DMP)	136 children Tested at the 7 to 9 years	Education, marital status, creatinine, housing status, child age, and three category race	No significant associations between prenatal DAPs, DEPs, or DMPs and total SRS *t*-scores In subgroups significant association between prenatal OP exposure and deficits in social functioning: Black DEP: Adjusted β = 5.1, 95% CI= 0.8, 9.4 Boys DEP: Adjusted β 3.5, 95% CI = 0.2, 6.8
Rauh (2006)	Prospective Cohort	BSID-II CBCL	Mother blood samples collected within 2 days after delivery	Chlorpyrifos	228 children Tested at 12,24,36 months	Prenatal environmental tobacco smoke exposure (ETS), gender, ethnicity, gestational age at birth, quality of the home care-taking environment, maternal educational level (high school degree versus no high school degree), and maternal IQ	Children (aged 3 y) exposed prenatally to high levels of chlorpyrifos pesticides (>6.17 pg/g plasma), as detected in samples of umbilical cord blood, significantly more likely to score in the clinical range for Pervasive Developmental Disorders (PDD) problems (aOR = 5.39;95% CI = 1.21–24.11) compared to thos4 exposed to low levels.
Sagiv (2018)	Cohort	SRS-2 at age14years BASC-2 ENI FERT, NEPSY-II	Mother urinary samples collected at 13-and26-week	DAP metabolites: 3 DMAP (DMP, DMTP, DMDTP) 3 DEAP (DEP, DETP, DEDTP)	534 children 247 ASD traits Tested at 7,10½,and14 years	Maternal age, education, country of birth, years in the United States, language of questionnaire, parity, marital status, depression, child's age at assessment, sex and quality of the home environment	Significant associations of prenatal urinary DAP metabolites with ASD-related traits at age 14 years

(continued)

Table 2a. (continued)

Author	Design	Diagnostic/ assessment method	Type of biological sample	Type of pesticide	Population	Confounding factors controlled for	Key findings
Shelton (2014)	Case control	ADI R, ADOS, SCQ, MSEL, VABS	Questionnaire self-reported exposure data	Organophosphate carbamate, pyrethroid insetticides, or organochlorine classes of pesticides	486 ASD children Mean age 36.7 ± 9.7 months 316 controls Mean age 36.9 ± 8.9 months	Paternal education, home ownership, maternal place of birth, child race/ ethnicity, maternal prenatal vitamin intake (during the 3 months before pregnancy through the first month), and year of birth	Mothers of children with ASD were 60% more likely to have organophosphates applied nearby the home during pregnancy (aOR = 1.60, 95% CI = 1.02–2.51) compared to mothers of TD children Significant associations between ASD and prenatal residential proximity to organophosphate pesticides in the third trimesters (organophosphates overall)
Philippat (2018)	cohort	ADI R SCQ MSEL ADOS	Mother urine collected during each trimester	Organophosphate pesticides DAP DEP DMP TCPy	203 mother-child pairs Tested at 3 years	home owner status, maternal BMI before pregnancy, season and date of birth	None of the OP metabolites assessed during pregnancy was significantly associated with increased risk of ASD at age 3 years when boys and girls were grouped together Trend for a significant association in girls.
Von Ehrenstein (2019)	Case control	ASD diagnosis collected by contracted regional centers	Information on all agricultural pesticides used within a specific geographic area	glyphosate, chlorpyrifos, diazinon, acephate, malathion, permethrin, bifenthrin, methyl bromide, imidacloprid, avermectin, and myclobutanil	2,516 ASD 3,5370 controls	Year of birth, sex, maternal race or ethnicity, maternal age, maternal education, and NOx (CALINE4) as a marker of traffic related air pollution	Risk of ASD disorder was significantly associated with prenatal exposure to: glyphosate (aOR = 1.16 95% CI = 1.06; 1.27) chlorpyrifos (aOR = 1.13 95% CI =1.05; 1.23) diazinon (aOR = 1.11 95% CI = 1.01; 1.21) malathion (aOR = 1.11 95% CI = 1.01; 1.22) And exposure during the first year of life to: glyphosate (aOR = 1.15 95% CI = 1.05; 1.26) chlorpyrifos (aOR = 1.10 95% CI = 1.02;1.20) malathion (aOR = 1.11 95% CI = 1.02;1.21) permethrin (aOR = 1.10 95% CI = 1.01;1.19)

Table 2b. Studies on ASD and Organochlorine//Polychlorinated Biphenyls (PCB) (studies listed by alphabetical order of first author's name).

Author	Design	Diagnostic/ assessment method	Type of biological sample	Type of pesticide	Population	Confounding factors controlled for	Key findings
Braun (2014)	Prospective cohort	SRS	Mother blood or urine samples woman 16 and 26 weeks of pregnancy	β-HCH	175 pairs of mother children Tested at 4 and 5 years	Maternal demographic and perinatal factors, including maternal age at delivery, race, marital status, education, parity, insurance status, employment, household income, and prenatal vitamin use	Detectable (vs. non- detectable) serum concentrations of PCB-178 (β = −3.0; 95% CI = −6.3, 0.2), β-hexachlorocyclohexane (β-HCH) (; β = −3.3; 95% CI = −6.1, −0.5), or PBDE-85 (*n* = 86; β = −3.1; 95% CI = −5.9 –0.5) were associated with lower ASD scores
Brown (2018)	Case control	ICD-10 criteria, validated with ADI R	Maternal serum	p,p:-DDE total PCB	775 ASD 778 controls	Maternal age, number of previous births, socioeconomic status, maternal and parental history of psychiatric disorders, and gestational week of the blood draw	p,p:-DDE significantly associated with autism diagnosis Unadjusted OR = 1.11, 95% CI = 1.11, 1.80; aOR = 1.32 95% CI = 1.02, 1.71
Cheslack-Postava (2013)	Case control	ADI-R	Mother blood samples collected during the first trimester	p,p:-DDE HCB	65 ASD 75 controls	Birth year, parental ages, sex and urbanicity mothers who experienced a prior pregnancy socioeconomic status	DDE and HCB not significantly associated with autism HCB = 1.29, 95% CI = 0.48, 3.45 DDE = 2.00, 95% CI = 0.60, 6.64 HCB aOR = 0.89, 95% CI = 0.28, 2.76 DDE aOR = 1.79, 95% CI = 0.51, 6.21) p0.36
Lyall (2017)	Case control	DSM-IV-TR	Mother serum and blood collected during 15–19 weeks gestation	PCB and 9 persistent pesticides [hexachlorobenzene, β-hexachloro-cyclohexane, γ-hexachlorocyclohexane, oxychlordane, *p,p´*–DDE, *p,p´*-DDT, and *o,p´*-DDT)	545 ASD children 418 controls Year of birth	Child sex, month, and year of birth), maternal age, maternal race/ethnicity (non-Hispanic white, Asian, black/Pacific Islander/or other, Hispanic, or missing), maternal weight at time of sample collection (quartiles), parity (multi- vs. primiparous), and maternal education (< high school, high school, college, graduate)	In both crude and adjusted models, several PCBs were significantly associated with increased risk of ASD (aORs) ~ 1.5 or greater for the top quartile. Strongest associations for PCB138/158 and PCB153 (for highest quartile relative to the lowest quartile, AOR = 1.79; 95% CI = 1.10, 2.92 and AOR = 1.82; 95% CI = 1.10, 3.02, respectively)
Roberts (2007)	Case control	DSM-IC-TR	Records from the California Department of Pesticide Regulation	Organochlorine pesticides	4,65 ASD children 6,975 controls	Maternal education, maternal race/ ethnicity, and regional center of diagnosis	The risk of ASD increased with the poundage of organochlorine applied and decreased with distance from field sites

Table 2c. Studies on ASD and Pyrethroids (studies listed by alphabetical order of first author's name).

Author	Design	Diagnostic/ assessment method	Type of biological sample	Type of pesticide	Population	Confounding factors controlled for	Key findings
Christian (2018)	Case control	CARS, ADOS, ADOS-2, ADI-R,	Questionnaire self-reported exposure data	Pyrethroids i	288 ASD 295 controls Age 2–8 years	Age of the mother, age of the father, father's education, and parish maternal exposures to fever over 101°F or infection requiring antibiotics, physical trauma, degreasers, oil-based paints, paint solvents	Maternal exposure to pesticides was associated with ASD in their children in the crude model (OR = 2.08 95% CI = 1.14, 3.08) and after adjusting for the child's parish (OR = 1.67 95% CI = 1.08, 2.59)
Domingues (2016)	Case control	ADOS, CARS	Child urinary and hair samples	Pyrethroids 3-PBA	21 ASD children Mean age 6.9years 19 controls Mean age 7.4 y		Higher (but not significantly) values of 3-BPA in children with ASD compared to the control group (p = .054). No significant correlation between CARS total score and 3-PBA in urine samples
Viel (2017)	Cohort	SDQ	Child and mother Urinary samples	3-PBA, 4-F-3-PBA, cis-DCCA and trans-DCCA, and cis-DBCA	287 children 6years	Age at the beginning of pregnancy, place of residence, parity, pre-pregnancy body mass index, education, WAIS-III score VIQ score, tobacco smoking at the beginning of pregnancy, usual fish consumption before pregnancy, length of pregnancy and breastfeeding, whether exclusive or not sex, birth weight, education, number of siblings at age 6, sleep duration, duration of television watching, duration of video game playing, regular extra-curricular sport activities and urinary cotinine concentration, HOME score when the child was 6 years of age (continuous), acid-leachable lead in the living room, number of smokers at home, and cigarettes smoked at home	PBA concentrations significantly associated with abnormal or borderline social behaviors on the SDQ (OR = 2.93, 95% CI =1.27, 6.78 and OR = 1.91; 95% CI = 0.80–4.57, for the intermediate and highest metabolite categories, respectively)
Von Ehrenstein (2019)	Case control	ASD diagnosis collected by contracted regional centers	Information on all agricultural pesticides used within a specific geographic area	glyphosate, chlorpyrifos, diazinon, acephate, malathion, permethrin, bifenthrin, methyl bromide, imidacloprid, avermectin, and myclobutanil	2,516 ASD 3,5370 controls	Year of birth, sex, maternal race or ethnicity, maternal age, maternal education, and NOx (CALINE4) as a marker of traffic related air pollution	Risk of ASD significantly associated with prenatal exposure to glyphosate, chlorpyrifos, diazinon, malathion, avermectin, and permethrin (OR = 1.10, 95% CI = 1.01, 1.20)

Table 2d. Studies on ASD and Avermectin (studies listed by alphabetical order of first author's name).

Author	Design	Diagnostic/assessment method	Type of biological sample	Type of pesticide	Population	Confounding factors controlled for	Key findings
Von Ehrenstein (2019)	Case control	California Department of Developmental Services (DDS), based on diagnostic data collected by contracted regional centers	information on all agricultural pesticide applications with the date, location, and amount of active ingredient applied	Glyphosate chlorpyrifos, diazinon, acephate, malathion, permethrin, bifenthrin, methyl bromide, imidacloprid, avermectin, and myclobutanil	2516 ASD 35370 controls Sample of 1998 to 2010 births	maternal age, indicators of socioeconomic status (that is, maternal race/ethnicity and education), and nitrogen oxides	Risk of ASD significantly associated with prenatal exposure to avermectin (OR = 1.11, 95% CI = 1.01, 1.22)

Table 2e. Studies on ASD and Imidacloprid (studies listed by alphabetical order of first author's name).

Author	Design	Diagnostic/ assessment method	Type of biological sample	Type of pesticide	Population	Confounding factors controlled for	Key findings
Keil (2014)	Case control	ADI R, ADOS, MSEL, VABS, SCQ	Questionnaire self-reported exposure data	Imidacloprid	262 controls 407 ASD	Maternal education, race/ethnicity, parity and pet ownership during pregnancy, child's sex and age at interview, and region of birth	No significant association between ASD diagnosis and prenatal imidacloprid exposure

ADI R = Autism Diagnostic Interview-Revised; ADOS = Autism Diagnostic Observation Schedule; ASD = autism spectrum disorder; BASC-PRS = Behavioral Assessment Scale for Children; BMI = Body Mass Index, ; CARS = Childhood Autism Rating Scale; CBCL = Child Behavior Checklist, ENI Evaluación Neuropsicológica Infantil; FERT = Facial Expression Recognition Test; HBRS = Hillside Behavior Rating Scale, ; HOME = Home Observation for Measurement of the Environment; MSEL = Mullen Scales of Early Learning; NEPSY-II = Developmental Neuoropsychological Assessment; PDD = Pervasive Developmental Disorder; PPVT = Peabody Picture Vocabulary Test; SDQ = Strengths and Difficulties Questionnaire; SRS = Social Responsiveness Scale; SCQ = Social Communications Questionnaire; VABS = Vineland Adaptive Behavioral Scale; VIQ = The Verbal,; WAIS-III = The Wechsler Adult Intelligence Scale—3rd revision IQ.
Chemical compounds: cis-DBCA cis-3-(2,2-dibromovinyl)- 2,2-dimethylcyclopropane-1-carboxylic acid, cis-DCCA cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid, DAP dialkylphosphate metabolites, DM dimethyl phosphate metabolites, DMAP Dimethyl Alkylphosphate molecules, DMP dimethylphosphate, DMTP dimethylthiophosphate, DMDTP dimethyldithiophosphate, DEP diethylphosphate, DEAP Diethyl Alkylphosphate molecules, DETP diethylthiophosphate, DEDTP diethyldithiophosphate, HCB hexachlorobenzene, MDA Malathion, PCBs polychlorinated biphenyls, p- p′-DDT p- p′- dichlorodiphenyltrichloroethane, p- p′-DDE p-p′-dichlorodiphenyldichloroethylene, HCB hexachlorobenzene, β-HCH β-hexachlorocyclohexane, trans-DCCA trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid, 3-PBA 3-phenoxybenzoic acid, 4-F-3-PBA 4-fluoro-3-phenoxybenzoic acid, TCPs Trichlorophenols, TCPy 3,5,6-trichloro-2-pyridinol.

Table 3. Newcastle Ottawa Scale Assessment for Case-control Studies.

	Selection				Comparability	Exposure		
Study	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of Exposure	Same method of ascertainment for cases and controls	Non-response rate
Bouchard (2010)	*	*	*	*	**	*	*	0
Braun (2014)	*	NA	*	0	NA	0	*	0
Brown (2018)	*	*	*	0	**	*	*	0
Cheslack-Postava (2013)	*	*	*	*	**	*	*	0
Christian (2018)	*	*	*	*	**	0	*	0
Domingues (2016) (A)	*	0	*	*	**	*	*	0
Domingues (2016) (B)	*	0	*	*	*	*	*	0
Eskenazi (2007)	*	0	*	*	**	*	*	0
Forns (2018)	*	0	*	*	**	*	0	0
Fortenberry (2014)	*	0	0	*	**	*	*	0
Furlong (2014)	0	NA	*	0	NA	0	*	0
Keil 2014	0	*	*	*	*	0	*	0
Lenters (2019)	*	*	*	*	**	*	*	0
Lyall (2017)	*	*	*	*	*	*	*	0
Marks (2010)	*	0	*	*	**	*	*	0
Oulhote (2013)	*	*	*	*	**	*	*	0

Note. NA = Not applicable.

Table 4. Newcastle Ottawa Scale assessment for Cohort Studies.

	Selection				Comparability	Outcome		
Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts
Philippat (2018)	0	NA	*	0	NA	*	*	*
Quiros-Alcala (2014)	*	*	*	*	**	*	*	0
Rauh (2006)	*	0	*	*	**	*	*	0
Roberts (2007)	0	*	*	0	0	0	*	0
Sagiv (2010)	*	0	*	*	**	*	*	0
Shelton (2014)	*	*	*	*	*	0	*	0
Sioen (2013)	*	0	*	*	**	*	*	0
van Wendel de Joode (2016)	*	0	0	*	**	*	*	0
Viel (2017)	*	*	*	0	0	0	*	0
Von Ehrenstein (2019)	0	*	0	0	*	0	*	0
Wagner-schuman (2015)	*	*	*	*	*	*	0	0
Xu (2011)	*	*	*	*	**	*	*	0
Yu (2016)	*	0	*	*	**	*	*	0

Note. NA = Not applicable.

exposure to 3, 5, 6-trichloro-2-pyridinol (TCPY) (a metabolite of chlorpyrifos and chlorpyrifos-methyl) and ADHD symptoms when considering all children combined. Of note, differently from the previous study (Rauh, 2006), urine samples were collected during the third trimester, rather than at delivery. However, there was a trend for significance for increased ADHD index in the highest TCPY tertile in boys ($p = .06$) and increased attention problems for the middle tertile in girls ($p = .08$).

Organochlorine pesticides and polychlorinated biphenyls (PCB). Overall, the association between ADHD and organochlorine pesticides/PCB is more uncertain than the link between ADHD and OPs. In a study in a cohort of 573 children (with completed data, out of an initial cohort of 607) with a prenatal exposure (evaluated with cord blood level) to polychlorinated biphenyl (PCB) and p,p'-dichlorodiphenyl dichloroethylene (p,p′-DDE) (Sagiv et al., 2010), a moderate significant association was found between levels of PCB or p,p′-DDE and ADHD symptoms rated with the Conners' Rating Scale for Teachers (CRS-T) (adjusted beta for the association between sum of 4 PCBs and Conners' ADHD index: 0.08, 95% CI = 0.03, 013; adjusted beta for the association between sum of p,p′-DDE and Conners' ADHD index: 0.01, 95% CI = 0.00, 003).

However, in the study by Sioen et al. (2013) pre-natal p,p′-DDE levels were not significantly associated with the hyperactivity score of the SDQ) at the age of 7 to 8 years in the whole sample (270 children), after adjustment for a number of variables (see Table 1) (aOR = 1.736, 95% CI = 0.849, 3.550). As noted above, the SDQ might not be sufficiently sensitive to specific behavioral ADHD-related problems. However, a lack of significant association with ADHD (defined based on a diagnosis reported in population-based registries or via questionnaires, including the SDQ and CBCL) was also reported in another study (Forns et al., 2018), in which the authors did not observe any significant association between either pre- or postnatal exposure (up to 24 months) to p,p′-DDE or hexachlorobenzene (HCB) and a diagnosis of ADHD, after adjusting for a number of variables (see Table 1). However, only one of the cohorts used relied on a specialist diagnosis recorded in population-based registries. Furthermore, differently from the previous studies, organochlorine pesticides in this study were measured in three different sources: maternal blood during pregnancy, cord blood and milk.

The study by Xu and colleagues (Xu et al., 2011), conducted in 2,539 children, focused specifically on trichlorophenols (TCPs). Compared with children with 2,4,6 TCP levels below the limit of detection (LOD), those with low (<3.58 mg/g) or high (>3.58 mg/g) levels of urinary 2,4,6-TCP were significantly more likely to have a parental reported diagnosis of ADHD (OR = 1.54; 95% CI = 0.97–2.43 and OR = 1.77; 1.18–2.66, respectively). Also, the authors found a significant linear association between 2,4,5-TCP, but not 2,4,5-TCP, and parent-reported diagnosis ADHD.

The findings by Lenters et al. (2019) are somehow at odds with the results of other studies. The authors assessed, among other compounds, five organochlorine pesticides (hexachlorobenzene HCB, β hexachlorocyclohexane β -HCH, oxychlordane, p,p′-dichlorodiphenyltrichloroethane p,p′-DDT and p,p′-DDE) in breast milk during the first two years of life in 1199 pairs mother-child. Whereas these authors found that breast milk concentrations of β-hexachlorocyclohexane (β-HCH) were significantly associated with increased odds of ADHD in childhood (median age 13 years), based on specialist diagnosis, (OR = 1.75; 95% CI = 1.22–2.53) in regression models, they also found an unexpected inverse associations between ADHD diagnosis and p,p′-DDT levels (OR = 0.64; 95% CI = 0.42–0.97), which the authors deemed to be due to live birth bias, unmeasured residual confounding or chance findings. Furthermore, HCB had a non-linear association with ADHD, with increasing risk in the low-level exposure range that switched to a decreasing risk at concentrations above 8 ng/g.

Pyrethroid insecticides. Findings are mixed also for this type of insecticide. In a cross-sectional study including 687 children from the 2001 to 2002 National Health and Nutrition Examination Survey, Wagner-Schuman et al. (2015) reported that the prevalence of ADHD was significantly higher in children who had detectable urinary levels of 3- phenoxybenzoic acid (3-PBA) compared to those with non-detectable levels (16.0% vs. 9.6%, $p = .03$). Furthermore, hyperactive-impulsive symptoms, but not inattentive symptoms, were significantly correlated with 3-PBA. In the above mentioned study by Oulhote and Bouchard (2013), the pyrethroid metabolite cis-DCCA in child urinary samples was found to be significantly associated with the total scores on the SDQ (OR for a 10-fold increase = 2.0; 95% CI = 1.1–3.6), while there was a nonsignificant association with other pyrethroid metabolites and no significant associations with the specific subscales of the SDQ were detected. However, in the study by Quiros-Alcala et al. (2014) in 1861 children, postnatal pyrethroid levels (3-PBA, cis- and trans- (2,2-dichlorovinyl)-2,2-dimethyl- cyclopropane-1-carboxylic acid, DCCA) were not significantly associated with parental report of ADHD and/or learning disability. Of note, the diagnosis of ADHD was based on parental/guardian report rather than based on school or medical records.

ASD

Organophosphate (OP). Similarly to what reported for ADHD, a number of studies provided evidence supporting

a significant association between organophosphate levels and ASD symptoms, although some negative studies were found.

In a prospective study of children (n =534) tested at 7, 10 1/2 and 14 years, Sagiv, Harris et al. (2018) found significant associations between maternal prenatal urinary dialkylphosphates (DAP) metabolites and ASD-related traits, measured with the Social Responsiveness Scale (SRS), at age 14 years. Prenatal DAPs levels were associated with poorer parent- and teacher-reported social behavior (a 10-fold DAP increase was associated with a 2.7-point increase (95% CI = 0.9–4.5) in parent-reported Social Responsiveness Scale,Version2,T-scores at age14).

Furthermore, Rauh et al. (2006) found that at 3 years of age, among 254 children, those who were exposed prenatally to high levels of chlorpyrifos pesticides (>6.17 pg/g plasma), as detected in samples of umbilical cord blood, were significantly more likely to score in the clinical range for Pervasive Developmental Disorders (PDD) problems (aOR = 5.39; 95% CI = 1.21–24.11), measured with the CBCL, compared to children with lower levels of chlorpyrifos exposure, after adjusting for a number of covariates (see Table 2).

Likewise, in another study, based on a total of 396 children, children with higher prenatal (maternal urine and serum samples during pregnancy, around 18 weeks of gestation) and postnatal (child urine samples) total DAPs were at significantly higher risk of ASD symptoms, as rated by mothers when the child was 2 years old on the CBCL, with an approximately 2-fold increase in risk for each 10-fold increase in metabolites (prenatal DAPs OR = 2.3; 95% CI = 1.0–5.2; 24-month DAPs OR = 1.7; 95% CI = 1.0–2.9) (Eskenazi, Marks et al., 2007). Additionally, prenatal dimethyl phosphate metabolites (one of the three measures DAPs) exposure to DE (another DAP) at 2 years were significantly associated with ASD symptoms at 2 years.

By contrast, another report based on 136 children (Furlong et al., 2014) found no significant associations between prenatal dialkylphosphate (DAP), or more specifically diethyl phosphates (DEP) and dimethylphosphate (DMP) and t-scores on the Social Responsiveness Scale (SRS). It is important to note that this scale does not provide a diagnosis of ASD and focuses on one aspect only of ASD. However, in multivariate adjusted models considering race as interaction term, increasing prenatal levels of DEP were associated with poorer scores on the SRS among blacks (β = 5.1 points, 95% CI = 0.8, 9.4), and among boys (β = 3.5 points, 95% CI = 0.2, 6.8), than girls (β = −.4 points, 95% CI = −4.1, 3.3).

Another apparently negative finding was provided by Philippat, Barkoski et al. (2018), who explored the possible association between OP (assessed in urine samples during the 2nd and 3rd trimester of pregnancy) and ASD diagnosed with gold-standard diagnostic tools (Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview-Revised). The study found no significant association between organophosphate metabolite concentrations and increased risk of ASD at age 3 years when boys and girls (total n = 203 pairs mother-child) were studied together. However, after stratification by sex, levels of DMTP during pregnancy tended to be associated with an increased ASD risk among girls (OR for a doubling in the DMTP concentration = 1.64; 95% CI = 0.95; 2.82) but not among boys (OR = 0.84; 95% CI = 0.63; 1.11).

Two studies focused on proximity to OPs during gestation, rather than measured levels of OPs. In the study by Shelton and colleagues (Shelton et al., 2014), the authors found that about one third of the 970 mothers who participated in their cross-sectional study lived, during pregnancy, close (within 1.5 km) to an agricultural pesticide application. The study showed that children of mothers who lived in proximity to OPs during pregnancy were 60% more likely to have ASD, and the risk was higher for third-trimester exposures (OR = 2.0; 95% CI = 1.1, 3.6), and second-trimester chlorpyrifos exposure (OR = 3.3; 95% CI = 1.5, 7.4). In the second study in 2516 children with ASD and 35,370 controls (von Ehrenstein et al., 2019), the risk of ASD was associated with prenatal exposure to glyphosate (aOR = 1.16; 95% CI = 1.06–1.27), chlorpyrifos (aOR = 1.13; 95% CI = 1.05–1.23), diazinon (aOR = 1.11; 95% CI = 1.01–1.21), and malathion (aOR = 1.11; 95% CI = 1.01–1.22) as well as to exposure, during the first year of life, to glyphosate (aOR = 1.15 95% CI = 1.05;1.26) chlorpyrifos (aOR = 1.10 95% CI = 1.02;1.20) malathion (aOR = 1.11 95% CI = 1.02;1.21) after controlling for socio-demographic and environmental variables (see Table 2).

Organochlorine pesticides and polychlorinated biphenyls (PCB). The majority of the studies retrieved in our systematic review point to a significant association between levels of organochlorine pesticides/PCB and ASD symptoms.

In a case-control study of 775 children diagnosed with ASD based on ICD-10 criteria and 778 matched controls, Brown et al. (2018) reported that the risk of ASD among offspring was significantly increased when maternal p,p'-DDE serum levels (measured in the first or second trimester of pregnancy) were in the highest 75th percentile, even after adjusting for maternal age, parity, and psychiatric history (aOR = 1.32; 95% CI = 1.02–1.71). In their study of 545 children with ASD and 418 controls, Lyall et al. (2017) also provided evidence supporting a possible role PCBs in the aetiology of ASD, with several PCBs (measured at 15–18 weeks gestation) being significantly associated with increased risk of ASD (aORs ~ 1.5 or greater for the top quartile).

Rather than measuring the levels of pesticides in biological samples, Roberts et al. (2007) assessed to which extent children with ASD where more likely than typically developing peers to live in areas near agricultural pesticides applications. In a sample including 465 children with ASD and 6,975 matched controls, they found that the risk of ASD increased with the poundage of organochlorine applied and decreased with distance from field sites.

However, a negative study and a study with unexpected results were also found. In the first one, Cheslack-Postava et al. (2013) did not find any significant difference between the levels of prenatal concentrations of dichlorodiphenyldichloroethylene (DDE) or hexachlorobenzene (HCB) in maternal blood samples during pregnancy between 75 cases with ASD, as per ICD-10 criteria, and 75 controls, even though, as noted by the authors, their sample size was limited.

Interestingly, in a follow-up of 222 mother-child pairs at 4 and 5 years of age, another study (Braun et al., 2014) reported fewer autistic behaviors (estimated with the Social Responsiveness Scale, SRS) among children born to women with detectable versus non-detectable blood urine concentrations of β-hexachlorocyclohexane (β = −3.3; 95% CI = −6.1–0.5) or PCB (β = −3.0; 95% CI = −6.3–0.2) measured in urine and serum at around 16 and 26 weeks of pregnancy. The authors suggested that contradictory results across studies "may be attributable to the different neurobehavioral domains assessed and differences in the timing of exposure assessment (e.g., prenatal vs. childhood) in these studies."

Pyrethroids. In a cross-sectional study using two datasets including a total of 298 pairs (case-controls) (Christian et al., 2018), self-report of maternal exposure to pesticides containing pyrethroids was significantly associated with a formal diagnosis of ASD diagnosis in the crude model (OR = 2.08; 95% CI = 1.14–3.08) as well as after adjusting for the child's parish (OR = 1.67; 95% CI = 1.08–2.59). In a small study (21 children with ASD and 19 controls) Domingues et al. (2016) reported higher, although marginally significantly, values of urine concentration of 3-Phenoxybenzoic-acid (3-BPA) in children with ASD compared to the control group ($p = 0.054$); no significant correlation between severity of ASD symptoms, measured with the CARS total score and (3-PBA) concentrations in urine samples. The small sample size prevents a firm interpretation of the findings.

A cohort study of 287 children (Viel et al., 2017) supported a significant association between abnormal or borderline social behavior (a dimension of ASD, but not equivalent to a formal diagnosis of ASD) evaluated with the SDQ and levels of one of the five pyrethroids measured in the study, that is, phenoxybenzoic acid (PBA) in child urine samples, (OR = 2.93; 95% CI = 1.27–6.78, and OR = 1.91; 95% CI = 0.80–4.57, for the intermediate and highest metabolite categories, respectively), but not with the maternal prenatal levels of pyrethroids.

In addition, in the above mentioned study by von Ehrenstein et al. (2019), the risk of ASD was significantly associated with prenatal exposure to permethrin (an insecticide in pyrethroid group) the during the first year of life (OR = 1.10; 95% CI = 1.01–1.20).

Avermectin. In the only study that we retrieved on this compound, by von Ehrenstein et al. (2019), increased risk of ASD was associated with prenatal exposure to avermectin (OR = 1.12; 95% CI = 1.04–1.22).

Imidacloprid. The only study that we found (Keil et al., 2014) showed a trend for a positive association (OR = 1.3; 95% CI = 0.78–2.2) between ASD diagnosis in children and mother self-report of prenatal imidacloprid exposure.

Discussion

To our knowledge, the present is the most updated and comprehensive systematic review on the relationship between ADHD or ASD and exposure to all kinds of pesticides. Overall, the included studies suggest that exposure to a number of (but not all) pesticides in different periods of pregnancy or in infancy/childhood may affect behavior and neurodevelopment in childhood. However, findings are not consistent as some negative studies were also found. Ideally, a meta-analytic approach would have been suitable to pool quantitatively the studies retained in our systematic review. However, given the heterogeneity of the studies, we did not deem appropriate to pool them meta-analytically. In fact, the studies were heterogeneous in a number of relevant aspects including, among others, type of pesticide, ways in which exposure was measured (in biological tissues or proximity to source of exposure), biological tissue in which the pesticide was measured, individual (child or mother) in which the pesticide levels were measured, study design (cross-sectional, cohort, case-control), diagnostic definition/procedure, focus on formal diagnosis as opposed to some symptoms of the disorder or general psychopathological aspects, exposure levels, timing of exposure, outcomes assessed, and age at assessment.

Even though the majority of the studies included in the systematic review did suggest a significant association between pesticides and ADHD/ASD symptoms, the strengths of the association and the possible confounders controlled for varied substantially across studies. Whilst sociodemographic factors and smoking during pregnancy have been generally controlled for across the majority of the retained studies, other possibly relevant variables, such as medications regularly taken by mothers during pregnancy or by the child, or use of illicit drugs during pregnancy, have not been controlled for systematically across studies.

Importantly, the evidence that we found in humans is not suitable to rigorously support a causal relationship between pesticides and ADHD/ASD. Evidence from animal studies does suggest possible causal role of pesticides in ADHD and/or ASD. Prenatal exposure even to low concentrations of chlorpyrifos has been shown to affects rodents' organogenesis (Tian et al., 2005) and lead to behavioral changes such as hyperactivity and working memory deficit. However, the exact mechanisms are far from being clear. Neurotransmitters including dopamine, noradrenaline, and serotonin, the primary target of ADHD pharmacologic treatments, are a possible target of pesticides. Less is known about the role of the cholinergic system. Although OPs pesticides at high doses would inhibit acetylcholinesterase, experimental evidence in animals suggests that even OPs doses that cause no or little cholinesterase inhibition may produce biochemical and behavioral effects (Costa, 2006, Middlemore-Risher et al., 2010). Other studies have explored the association of pesticide exposure and children developing ADHD; possible mechanisms include reduced muscarinic receptors and a7 nicotinic acetylcholine receptor (nAChR) expression, DNA replication disruption, incremental oxidative stress, and excitatory effects in the brain (Eskenazi et al., 1999; Howard et al., 2005; Middlemore-Risher et al. 2010; Slotkin & Seidler, 2009).

In relation to ASD, Abou-Donia et al. (2008) noted that prenatally exposed rats displayed sensorimotor deficits and increased expression of glial fibrillary acidic protein, which has been previously reported among individuals with ASD (Ahlsen et al. [1993] and Rosengren et al. [1992]), and in a mouse model for ASD (Fatemi et al., 2005). Furthermore, both dicofol and endosulfan noncompetitively bind gamma amino-butyric acid (GABA) receptor–mediated chloride ion channels in nerve cells (Sunol et al., 1998). GABA-mediated neurotransmission is known to play important roles in gestational brain development, and the theory that altered GABA metabolism could play a role in ASD has been proposed (Cohen, 2001).

The present systematic review should be considered in the light of limitations of individual studies included in it as well as of possible limitations of the systematic review itself. As shown by the NOS assessment, "non-response rate" for case-control studies and "Adequacy of follow up of cohorts" for cohort studies were rated at risk in 100% and 95% of the included case-control and cohort studies, which is a clear limitation that should be taken into account when interpreting the results. In addition, a number of studies (see Tables 1 and 2) had a relatively small sample size, which could underestimate the magnitude of the associations or lead to spurious findings.

Furthermore, from a methodological standpoint, studies based on spot urine samples may not represent a child's average exposure over time and may result in misclassification, reducing the statistical power to detect associations. Moreover, many of them are not based on measure of long-term exposure but on one spot of urine only (urinary levels may reflect recent exposure).

Another issue is that ingestion of preformed metabolites from food and other sources exposure could be a cause of misclassification and most of the studies did not consider genetic and other factors related to metabolism. Interestingly, it has been found that different paraoxonase-1 (PON1) polymorphisms may affect neurodevelopment in children. Certain genotypes (PON1–108TT, PON1192QRand PON1192RR) may be associated with reduced mental and motor development in children exposed to OP pesticides (Engel et al., 2011; Eskenazi et al., 2004)

In terms of the possible limitations of the systematic review, although we endeavoured to conduct a systematic search in multiple databases with no data or language limitations, we can not exclude we missed relevant papers. Also, even though we used a comprehensive set of search terms, we might have missed some compounds.

Conclusion and Future Perspectives

The majority of the studies included in this systematic review suggest a significant association between exposure to pesticides/agrotoxics and ADHD or ASD, albeit their results should be considered with caution due to a number of methodological issues. Given the widespread use of pesticides in agriculture and its increasing detection in food and water, additional studies on the human health effects of chronic (non-acute) pesticides exposure are an important public health need.

Future studies should use a prospective design, with multiple biological samples collected over time for the better assessment of exposure and its critical windows. Moreover, additional research should investigate the potential susceptibilities to toxicants implicated in some individuals - including altered detoxification, genetic factors, oxidative stress, altered neuronal development and synaptic function, and hormonal factors- could act synergistically and amplify the adverse effects of toxicants during critical periods of neurodevelopment particularly during the prenatal and early postnatal periods. Additionally, further research is needed to improve understanding of whether repeated exposures over time or just short-term exposures during critical windows of development is related to neurodevelopmental alterations.

We conclude that, whilst there is some evidence suggesting a possible link between exposure to pesticides and ADHD or ASD, current literature is still in its infancy and a more rigorous research approach is needed.

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