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# REVIEW OF CURRENT EVIDENCE ON THE IMPACT OF PESTICIDES, POLYCHLORINATED BIPHENYLS AND SELECTED METALS ON ATTENTION DEFICIT / HYPERACTIVITY DISORDER IN CHILDREN

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**Abstract**
The aim of this review was to investigate the association between attention deficit / hyperactivity disorder (ADHD) or ADHD-related symptoms and industrial chemicals, such as organophosphates and organochlorine pesticides, polychlorinated biphenyls (PCBs), lead, mercury and manganese. Medline, PubMed and EBSCO searches were performed to identify the studies that analyzed the association of prenatal and postnatal child exposure to such toxicants and ADHD or ADHD-related symptoms. The review is restricted to human studies published in English in peer-reviewed journals since 2000. Most of the presented studies focused on pesticides, PCB and lead. The impact of mercury and manganese was investigated less frequently. The findings indicate that children's exposure to organophosphate pesticides may cause symptoms consistent with pervasive developmental disorder, ADHD or attention problems. Exposures to organochlorine pesticides and PCBs were associated with ADHD-like behaviors such as alertness, quality of alert response, and cost of attention. The studies provided evidence that blood lead level below 10 μg/dl was associated with ADHD or ADHD-related symptoms. Information on the association between exposure to mercury and neurotoxicity is limited, and requires further confirmation in future research. Two studies indicated that exposure to manganese is related to ADHD; such exposure and its impact on children neurodevelopment need to be further investigated. Future studies should use a prospective design with multiple biological samples collected over time for better assessment of exposure and its critical windows. Additionally, inclusion of potential confounding factors and co-exposures is crucial.

**Key words:**
**Children, Chemicals, Attention deficit / hyperactivity disorder, Inattention, Impulsivity**

## INTRODUCTION

In recent years, increasing awareness has been observed concerning the role of different toxicants in neurodevelopmental disorders, including attention-deficit / hyperactivity disorder (ADHD). Developmentally inappropriate high levels of inattention, impulsivity, and hyperactivity are characteristics of ADHD according to DSM-IV [1–3]. Current ICD-10 uses a different name, hyperkinetic disorder (HD), but it provides very similar symptoms for this disorder [4]. Regardless of the name used, ADHD/HD is one of the most common neurobehavioral disorders in childhood, affecting 3–10% of children worldwide [1,2].

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Symptoms of ADHD often persist into adolescence and adulthood, and are associated with substantial social and medical costs. ADHD is a highly heritable disorder, with pooled data from twin studies suggesting a heritability rate of 76% [5]. Emerging evidence indicates that neurodevelopmental disorders, including ADHD, result from complex interactions of genetic, environmental, and social factors. The developing brain is uniquely vulnerable to neurotoxins at exposure levels that have no lasting effects on adults. Although public health activities and regulatory initiatives limiting the level of exposure to industrial chemicals are remarkably successful, there are still concerns of their impact, even at low level, on children's health and neurodevelopment.

This paper reviews literature published since 2000 investigating the association between ADHD or ADHD-related symptoms and industrial chemicals, such as organophosphates and organochlorine pesticides, polychlorinated biphenyls (PCBs), heavy metals, and manganese.

**Criteria of the selection of studies to the review**

Medline, PubMed and EBSCO searches were performed to identify studies that analyzed the association of prenatal and postnatal children's exposure to industrial chemicals and ADHD or ADHD-related symptoms. Relevant studies were also identified via a review of references cited in published studies. The review is restricted to human studies published in peer-reviewed English journals since 2000. The following keywords were used: ADHD, hyperactivity, inattention, impulsivity, pregnancy, prenatal period, child, environmental exposures, industrial chemicals, organophosphate pesticides, organochlorine pesticides, PCBs, heavy metals, lead, mercury, and manganese. The following information was reviewed from each paper, which met the eligible criteria: study design and population, sources of exposure and methods used for its assessment, methods of assessment of ADHD or ADHD-related symptoms and confounding factors included in analysis.

Out of the total 95 identified articles, 31 met the eligibility criteria and were included in the present review.

**Organophosphates pesticides and ADHD or ADHD-related symptoms**

Organophosphate (OP) pesticides are a group of insecticides commonly used for agricultural purposes. OP pesticides are potent toxicants that target the nervous systems of insects and other pests [7]. Exposure to some of these organophosphate compounds was shown to cause hyperactivity and cognitive deficits in animal studies [8]. Recent studies have shown that fetuses and young children have lower levels of detoxifying enzymes (paraoxonase or chlorpyrifos-oxonase) that deactivate OP [9,10] than adults, suggesting that they may be more vulnerable to these exposures.

Several biological mechanisms might cause an association between OP pesticides and ADHD. The primary action of organophosphates, particularly with respect to acute poisoning, is inhibition of acetylcholinesterase [11], and disruptions in cholinergic signaling [12]. At doses lower than those inhibiting acetylcholinesterase, certain organophosphates affect different neurochemical targets, several neurotransmitter and second messenger systems, including growth factors [13,14]. Developmental exposure to organophosphates might have persistent effects on multiple neural systems that may cause ADHD behaviors, such as inattention and cognitive deficits, similar to the effects of developmental nicotine exposure [15,16].

The associations between organophosphate pesticides, ADHD and attention-related outcomes were examined in five studies performed in the United States among young children [17–21] (Table 1).

Rauh et al. [17] found that concentrations of chlorpyrifos in maternal serum were consistently associated with the mothers' report of symptoms of pervasive developmental disorder (PDD) as well as that of attention deficit / hyperactivity disorder (ADHD) or attention problems. Mental

**Table 1.** Exposure to organophosphate pesticides and ADHD or ADHD-related symptoms

| Country | Study population | Type of study | Definition of exposure | Test used | Confounding factors | Results | References |
|---|---|---|---|---|---|---|---|
| The United States, California, Salinas Valley – The Centre for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) | 396 children at 6 months<br>395 children at 12 months<br>372 children at 24 months | Cohort | Six DAP metabolites in maternal and child urine: a) three DM metabolites (DMP, DMTP, DMDTP), b) three DE metabolites (D EP, DETP, DEDTP) | Bayley Scales of Infant Development, Child Behavior Checklist (CBCL) | Psychometrican, location, age at assessment, sex, breast-feeding duration, HOME, household income above poverty threshold, parity | Pregnancy DAP levels were negatively associated with MDI. Neither prenatal nor child DAPs were associated with PDI or CBCL attention problems, but both prenatal and postnatal DAPs were associated with the risk of pervasive developmental disorder | Eskenazi 2007 [18] |
| | 331 children assessed at 3.5 years of age and 323 children assessed at 5 years of age | | | Child Behavior Checklist (CBCL), Visual Attention subtest (NEPSY-II), Conners' Kiddie Continuous Performance Test (K-CPT) | Age at assessment, child care, breastfeeding, maternal education, depressive symptoms | Prenatal DAPs were not significantly associated with maternal report of attention problems and ADHD at the age of 3.5 years, but were significantly related at the age of 5 years with attention problems and ADHD | Marks 2010 [20] |
| The Unites States, Yuma County, Arizona – The Children Pesticide Survey of Southern Arizona | 48 children at 7 years of age – 25 exposed to OP pesticides and 23 unexposed to OP pesticides according to urine analysis | Cross-sectional | OP metabolites in children urine: DMP, DMTP, DMDTP, DEP, DETP, DEDTP | Wisconsin Card Sorting Test (WCST), Weschsler Intelligence Scale for Children – third edition (WISC-III), Children's Memory Scale, Trail Making Test A and B, Child Behavior Checklist | None | Adverse associations of child urinary DAPs and attention-related performance errors | Sanchez-Lizzardi 2008 [21] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| The Unites States, The National Health and Nutrition Surveys (NHANES) – data from years 2000–2004 | 1 139 children 8–15 years of age – 119 children met the diagnostic criteria for ADHD | Cross-sectional | Urinary concentrations of dialkyl phosphate metabolites (DAP): three dimethyl alkylphospahte (DMP, DMTP, DMDP), 3 diethyl alkylophosphate (DEP, DETP, DEDTP) | DSM-IV | Gender, age, race/ethnicity, poverty/income ratio, fasting duration | Children with higher urinary dialkyl phosphate concentrations, especially DMAP concentrations, were more likely to be diagnosed as having ADHD. A 10-fold increase in DMAP was associated with ADHD (OR = 1.55; 95% CI: 1.14–2.10); for DMAP, children with levels higher than the median of detectable concentrations had twice the odds of ADHD (OR = 1.93; 95% CI: 1.23–3.02), compared with children with the undetectable levels | Bouchard 2010 [19] |
| The Unites States, New York – prospective cohort of inner-city mothers and their newborn infants | 254 children evaluated throughout the first 3 years of life (12, 24, 36 months of life) | Cohort | Chlorpyrifos levels in the umbilical cord plasma | Bayley Scales of Infant Development II, Child Behavior Checklist | Prenatal ETS exposure, gender, ethnicity, gestational age at birth, quality of the home care-taking environment, maternal education level, maternal IQ | High prenatal level of chlorpyrifos (> 6.17 pg/g plasma), reported more attention problems and symptoms of pervasive developmental disorders at 3 years of age | Rauh 2006 [17] |

DM – dimethyl phosphate metabolites; DE – diethyl phosphate metabolites; DAP – dialkyl phosphate metabolites; DMP – dimethylphosphate; DMTP – dimethylthiophosphate; DMDTP – dimethyldithiophosphate; DEP – diethylphosphate; DETP – diethylthiophosphate; DEDTP – diethyldithiophosphate; DMAP – dimethyl alkylphosphate; DEAP – diethyl alkylphosphate.
OR – odds ratio; CI – confidence interval; ADHD – attention-deficit / hyperactivity disorder.
MDI – mental development index; PDI – psychomotor development index.
HOME – Home Observation for Measurement of the Environment.

and psychomotor developments were also investigated in a cohort of farmworkers' children living in the Salinas Valley of California [18]. In the study, adverse associations of prenatal OP metabolites with mental development and pervasive development disorders at 24 months of age were observed. The same cohort study of children assessed at 3.5 and 5 years of age, showed exposures to dialkyl phosphates (DAPs) that were adversely associated with attention as assessed by maternal report, psychometrician observation, and direct assessment. These associations were slightly stronger at 5 years than at 3.5 years of age and were stronger in boys [20].

A recent cross-sectional study reported associations between child OP metabolite concentrations and ADHD in 8- to 15-year-olds characteristic (or typical) of the U.S. population [19]. Children with higher urinary dialkyl phosphate concentrations, especially dimethyl alkylphosphate (DMAP) concentrations, were more likely to be diagnosed with ADHD. For the DMAP metabolite, children with levels higher than the median of detectable concentrations had a twice higher chance of having ADHD, compared with children with the undetectable levels [19]. Adverse associations of child urinary DAPs and attention-related performance errors on the Wisconsin Card Sorting Test were reported in another cross-sectional study of Hispanic children living in an agricultural community [21]. The findings of the reviewed studies indicate that children's exposure to organophosphate pesticides may cause symptoms consistent with pervasive developmental disorder (PDD) [8,17] as well as attention deficit / hyperactivity disorder (ADHD) [17,19,20] or attention problems [17,20,21].

**Organochlorine pesticides and polychlorinated biphenyls and ADHD or ADHD-related symptoms**

Organochlorines, including polychlorinated biphenyls (PCBs) and *p,p*'-dichlorodiphenyl dichloroethylene (*p,p*'-DDE), are environmentally persistent contaminants that readily cross the placenta, posing a potential risk to the developing fetus. Associations of PCBs with ADHD-like behaviors have been observed in rodents and nonhuman primates [22–24]. There is a lack of sufficient knowledge of the biologic mechanism for the observed effect of PCBs and organocholrine pesticides on ADHD and attention in humans [25]. PCBs can disrupt dopaminergic functions, as reflected in alterations in dopamine levels in the cell culture and in the brains of laboratory animals [26,27]; this is one possible mechanism whereby PCBs may affect attention-related behaviors, since decreases in cellular dopamine have been correlated with attention disorders such as ADHD [28].

A number of epidemiological studies, which assess the neuropsychological consequences of exposure to PCBs, have been performed over the last 11 years [29–35] (Table 2). Only two studies have examined the association between cord PCBs and organochlorine pesticides (*p,p*'-DDE) and the risk of ADHD-related behaviors [25,36] (Table 2).

The Netherlands Cohort Study found associations between PCBs and a longer response time and more variations in the response time among 9-year-olds [29]. A study of children born to Lake Michigan fish consumers reported associations between prenatal PCB exposure and poorer concentration and verbal, pictorial and auditory working memory among 11-year-old children; the examined children also demonstrated greater impulsivity [30].

Investigators from the Oswego Newborn and Infant Development Project reported associations between prenatal PCBs and errors of commission (false – positive responses) on the Continuous Performance Test at 4.5, 8, and 9.5 years of age, suggesting potential impairment of response inhibition [31,32]. The suggestion of potential impairment was supported by observing associations of PCBs with poorer performance on the Differential Reinforcement of Low Rates of Response test (in the same cohort study at the age of 9.5 years), which measures the

**Table 2.** Exposure to organochlorine pesticides and polychlorinated biphenyls and ADHD or ADHD-related symptoms

| Country | Study population | Type of study | Definition of exposure | Test used | Confounding factors | Results | References |
|---|---|---|---|---|---|---|---|
| The United States, The National Health and Nutrition Surveys (NHANES) – data from the years 1999–2000 | 278 children aged 12–15 years | Cross-sectional | POPS analyzed in children blood: PCB126, HPCDD, OCDD, HPCDF, HCH, p,p-DDE, TNA | Disability and attention deficit disorder reported by the parents; no neurodevelopmental test used | Age, race, sex, poverty index ratio, mother's age at pregnancy, birth weight, smoking during pregnancy, BMI, saturated fat intake | No significant association between PCB and ADHD | Lee 2007 [35] |
| The United States, New Bedford, Massachusetts | 788 infants (5–22 days) residing near a PCB-contaminated harbor and Superfund site in New Bedford, Massachusetts | Cohort | Cord serum level of the 51 individual PCB congeners and two chlorinated pesticides (*p,p'*-DDE, HCB) | Neonatal Behavioral Assessment Scale (NBAS) | Infant's age at exam, birth year, time since last feeding, NBAS examiner and maternal age, education, breast-feeding, household income | Inverse associations between the cord serum PCB and DDE levels and alertness, quality of alert responsiveness, cost of attention | Sagiv 2008 [25] |
| | 607 children aged 7–11 years residing near a PCB-contaminated harbor in New Bedford, Massachusetts | | Umbilical cord serum level of the sum of 4 prevalent PCB congeners (118, 138, 153, 180) and *p,p'*-DDE level | Conners' Rating Scales for Teachers | Child's age, child's sex, maternal age, marital status, smoking during pregnancy, alcohol consumption during pregnancy, illicit drug use | Higher risk for ADHD-like behaviors at levels (> 1.26 ng/g lipid) of the sum of 4 PCBs. Higher risk for ADHD-like behaviors at levels (> 1.58 ng/g lipid) of *p,p'*-DDE | Sagiv 2010 [36] |
| The United States, Michigan, Michigan Lake | The United States, Michigan, 154 children assessed at 4 years of age, 148 children at 11 years of age | Cohort | Umbilical cord serum, maternal serum and milk concentration of PCBs | Continuous Performance Test (CPT), Digit Cancellation, Wisconsin Card Sorting Test, Sternberg Memory Paradigm, Wechsler Intelligence Scale for Children-Revised (WISC-R) | SES, mother's age at child's birth, marital status, child's sex, parity, maternal education, HOME scores, maternal drinking and smoking during and after pregnancy, delivery complications | Prenatal PCB exposure was associated with greater impulsivity, poorer concentration, and poorer verbal, pictorial, and auditory working memory | Jacobson 2003 [30] |

**Table 2.** Exposure to organochlorine pesticides and polychlorinated biphenyls and ADHD or ADHD-related symptoms – cont.

| Country | Study population | Type of study | Definition of exposure | Test used | Confounding factors | Results | References |
|---|---|---|---|---|---|---|---|
| The United States, Oswego, New York, Ontario Lake – The Oswego Newborn and Infant Development Project | 189 children assessed at 4.5 years of age | Cohort | Umbilical cord blood level of PCBs, maternal hair mercury, postnatal Pb exposure (venous blood) | McCarthy Scales of Children's Abilities,<br>Catch-the-Cat Test | SES, maternal IQ, maternal education, home environment, smoking | A dose-dependent association between cord blood PCBs and errors of commission | Stewart 2003 [31] |
| | 202 children assessed at 8 years of age and later at 9.5 years of age | Cohort | Umbilical cord blood level of PCBs, postnatal Pb exposure (venous blood), methylmercury (MeHg) in hair | Continuous Performance Test (CPT),<br>Extended Continuous Performance Test (E-CPT) | Maternal IQ, maternal sustained attention and maternal response inhibition, SES, maternal education | Prenatal PCB exposure was associated with increased impulsive responding on CPT | Stewart 2005 [32] |
| | 167 children assessed at 9.5 years of age | Cohort | Umbilical cord blood level of PCBs, methylmercury (MeHg) in hair, postnatal PB exposure (venous blood) | Differential Reinforcement of Low Rates task (DRL) | HOME, SES, maternal IQ, maternal education, paternal education | Children prenatally exposed to PCBs responded excessively, with significantly lower interresponse time and fewer reinforcers earned across the session | Stewart 2006 [33] |
| Europe, The Faroese Island | 435 children at 7 years of age | Cohort | PCBs was examined by the analysis of cord tissue<br>Cord Blood Hg | Neurobehavioral Evaluation System (NES2), Finger Tapping Test<br>NES2 Hand–Eye Coordination Test<br>NES2 Continuous Performance Test<br>Wechsler Intelligence Scale for Children-Revised<br>(WISC-R) Digit Spans<br>WISC-R Similarities<br>WISC-R Block Designs<br>Bender Visual Motor Gestalt Test<br>California Verbal Learning Test (Children)<br>Boston Naming Test<br>Neurophysiological and sensory tests | Sex, age, maternal score on Raven's Progressive Matrices, medical risk for neurobehavioral deficit, maternal and paternal education level, paternal employment, day care | Among 17 neuropsychological outcomes determined at the age of 7 years, the cord PCB concentration was associated with deficits within the highest tertile of mercury exposure on the Boston Naming Test, the Continuous Performance Test reaction time ($p = 0.03$) | Grandjean 2001 [34] |

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|---|---|---|---|---|---|---|
| Europe, The Netherlands – The Netherlands Cohort Study | 207 children at the age of 9 | Cohort | Sum of PCB 118, 138, 153 and 180 in maternal and cord plasma and breast milk | Tower of London (TOL) | Type of feeding, duration of breastfeeding, sex, parity, parental education level, parental verbal IQ, HOME, age at examination | Higher prenatal PCB levels were associated with longer response times (RTs), more variation in RTs, and lower scores on the Tower of London (TOL) | Vreugdenhil 2004 [29] |

PCB126 – 3,39,4,49,5-pentachlorobiphenyl; HPCDD – 1,2,3,4,6,7,8-heptachlorodibenzo- p-dioxin; OCDD – 1,2,3,4,6,7,8,9-octachlorodibenzo-pdioxin; HPCDF – 1,2,3,4,6,7,8-heptachlorodibenzofuran; HCH – b-hexachlorocyclohexane; p,p-DDE – p,p9-dichlorodiphenyltrichloroethane; TNA – trans-nonachlor; HCB – hexachlorobenzen; PCB 118 – 2,3',4,4'5-pentachlorobiphenyl; PCB 138 – 2,2',3,4,4',5'-hexachlorobiphenyl; PCb 153-2,2',4,4',5,5'-hexachlorobiphenyl; PCB 180 – 2,2',3,4,4',5,5'-heptachlorobiphenyl; SES – socioeconomic status.
Other abbreviations as in Table 1.

ability to withhold a rewarded response for a specific time delay [33]. The Faroe Islands study found associations between PCBs and attention measured by the Continuous Performance Test among children aged 7 years only in the context of high mercury exposure, suggesting a potential interaction between these contaminants [34].

Conversely, the study by Lee et al. [35] among 278 children aged 12–15 years did not find a link between the current child PCB levels and the attention deficit disorder.

To investigate an association between cord serum polychlorinated biphenyls (PCBs) and *p,p'*-DDE levels and measures of attention, Sagiv et al. [25] performed a study among 788 infants (5–22 days) born in the years 1993–1998 to mothers residing near a PCB-contaminated harbor and the Superfund site in New Bedford, Massachusetts. Consistent inverse associations between cord serum PCB and DDE levels and alertness, quality of alert responsiveness, cost of attention, and other potential attention-associated measures including self-quieting and motor maturity were observed [25]. The following study performed by Sagiv et al. [36] assessed the exposure to PCBs and DDE and ADHD among children aged 7–11 years from the same cohort study. The authors found higher risk for ADHD-like behaviors at the levels of *p,p'*-DDE (> 1.58 ng/g lipid) and the levels of the sum of 4 PCBs (> 1.26 ng/g lipid).

The outcome of the presented studies has proven an association between exposure to organochlorine pesticides and PCBs and ADHD-like behaviors: alertness, quality of alert responsiveness, cost of attention, and other potential attention-associated measures including self-quieting and motor maturity [25,36]. In addition, studies found that exposure to PCBs can be linked with a longer, more variant response time, impairment of response inhibition [31–33], poorer concentration and verbal, pictorial and auditory working memory [30] and attention problems [34]. Only one study did not find an association between ADHD and ADHD-like behaviors and PCBs exposure [35].

**Mercury and ADHD or ADHD-related symptoms**

There are three basic forms of mercury: elemental, inorganic and organic. Deep-sea fish are commonly contaminated with organic methylmercury, which may be toxic to the brain when a moderate to large amount is ingested [37]. So far, there is scarce evidence on mercury-related ADHD behaviors in children, especially in areas with relatively low fish consumption. Mercury can adversely affect enzymes, the cellular membrane function, and neurotransmitter levels [38,39]. Mercury causes oxidative stress, lipid peroxidation, and mitochondrial dysfunction and disrupts synaptic transmission, microtubule formation, amino acid transport, and cellular migration in the developing brain [40], which can be associated with neurodevelopmental problems in children.

Studies, which investigated the possible link between exposure to mercury and ADHD or ADHD-related behaviors, were performed in China [37], Romania [41], South Korea [42], Faroe Islands [43,44], and in the Republic of Seychelles [45] (Table 3).

In a study performed in China, children with blood mercury level above 29 nmol/l had almost a 10-time higher risk of having ADHD after adjustment for confounding variables [37]. The ADHD behaviors were evaluated in the study performed in Faroe Islands among 14-year-old adolescents. Indicators of prenatal methylmercury exposure were significantly associated with deficits in finger tapping speed, reaction time on a continued performance task, and cued naming [43]. Additionally, among the same cohort of children in Faroe Islands, sustained attention was influenced by the prenatal methylmercury exposure [44]. The study performed by Myers et al. [45] in the Republic of Seychelles among 9-year-old children reported decreased performance in the grooved pegboard using the non-dominant hand in males, and improved scores in the hyperactivity index of the Conner's teacher rating scale associated with exposure to mercury (Table 3).

Conversely, Nicolescu et al. [41] did not find a significant association between concurrent mercury levels and ADHD symptom scores in a cross-sectional study of Romanian children. The findings are in agreement with the study of bigger sample sizes that did not find a significant relationship between mercury exposure and ADHD-related outcomes [42].

The results of the studies presented above are inconsistent. Ha [42] and Nicolescu [42] did not find a significant relationship between mercury exposure and ADHD, whereas Cheuk [37] found higher risk of ADHD among children with exposure to mercury.

Some studies suggest a link between exposure to mercury and ADHD behaviors: increased hyperactivity scores [45], sustained attention [44] and deficits in finger tapping speed and reaction time [43], but as the number of studies is rather limited, the observations need to be confirmed in other epidemiological studies.

**Lead and ADHD or ADHD-related symptoms**

Lead is one of well-established environmental toxicants, and its adverse effects, particularly in children, continue to be a major public health issue worldwide. It is well known that lead can cause cognitive impairment and correlate with decreased IQ scores and impaired attention. The World Health Organization and U.S. Centers for Disease Control and Prevention recommended that child blood lead levels not exceed 10 μg/dl [46]. Furthermore, recent studies have shown that cognitive deficits and behavioral problems in children still exist, even with blood lead level < 10 μg/dl, and that no threshold below which lead does not cause neurodevelopmental toxicity can be defended [46,47].

Lead is a potent developmental neurotoxin that can affect multiple neurochemical pathways and interfere with blood-brain capillary integrity, synaptogenesis, myelination, and catecholamine metabolism in the central nervous system [48]. These multiple potent effects occur in

**Table 3.** Exposure to mercury and ADHD or ADHD-related symptoms

| Country | Study population | Type of study | Definition of exposure | Test used | Confounding factors | Results | References |
|---|---|---|---|---|---|---|---|
| The Republic of Seychelles | 717 children at the age of 9 years | Cohort | Prenatal Me Hg exposure was determined from maternal hair growing during pregnancy, postnatal-children hair | The Wechsler intelligence scale for children, the Woodcock-Johnson test of achievement, Letter-word recognition, Applied problems subtests, California verbal learning test, The visual memory subtest of the wide-range assessment of memory and learning, finger tapping, Trailmaking, Grooved pegboard, Bruininks-Oseretsky test of motor proficiency, Boston naming test, The Beery-Buktenica developmental test of visual motor integration, Test of haptic matching, Connor's continuous performance test | Maternal IQ, home environment, child's age, socioeconomic scores | Increased exposure was associated with decreased performance in the grooved pegboard using the non-dominant hand in males and improved scores in the hyperactivity index of the Conner's teacher rating scale | Myers 2003 [45] |
| Europe, Romania | 83 children aged 8–12 years old | Cross-sectional study | Blood mercury, Pb, Al level in children | German "Testbatteriezur Aufmerksamkeitsprüfung für Kinder – KITAP" (test battery for attention performance of children), behavioral rating scales | Gender, age, computer experience, handedness, eye problems, number of siblings, parental education, smoking/alcohol in pregnancy, family psychopathology, study area | No significant association between mercury levels and ADHD | Nicolescu 2010 [41] |

**Table 3.** Exposure to mercury and ADHD or ADHD-related symptoms – cont.

| Country | Study population | Type of study | Definition of exposure | Test used | Confounding factors | Results | References |
|---|---|---|---|---|---|---|---|
| Europe, The Faroe Islands | 878 adolescents at the age of 14 years | Cohort | Blood and hair samples from the participants were analyzed for mercury | Neuropsychological Examination System (NES2), Continuous Performance Test (CPT), The Catsys® equipment, Wechsler Intelligence Scale for Children-Revised (WISC-R), Block Designs, Stanford-Binet Copying Children's Category Test, Wechsler Memory Scale – III (WMS-III) Spatial Span | Age, sex, maternal Raven score, residence in town/village, school grade, maternal and paternal employment, time of day, language, and computer experience | Prenatal methylmercury exposure was significantly associated with deficits in finger tapping speed, reaction time on a continued performance task | Debes 2006 [43] |
| | 878 adolescents at the age of 14 years | Cohort | Mercury level in cord blood and maternal hair | Continuous Performance Test | Age, sex, school grade, maternal and paternal employment, time of day, language, hand dominance and computer experience | Impact of methylmercury exposure on sustained attention | Julvez 2010 [44] |
| China, Hong Kong | 52 children with ADHD aged below 18; 59 controls | Case-control | Blood mercury level in children | Diagnostic and Statistical Manual of Mental Disorders-IV (DSMIV) | Age, gender, parental occupational status | Children with blood mercury level above 29 nmol/l had 9.69 times (95% CI: 2.57–36.5) higher risk of having ADHD | Cheuk 2006 [37] |
| South Korea – The Children's Health and Environment Research (CHEER) | 1778 children at 10 elementary schools in six South Korean cities | Cohort | Mercury and lead level in children | The Korean version of the abbreviated Conners' scale for ADHD symptom screening | Age, gender, household income, parental history of neuropsychiatric diseases and residential area, blood lead level | No significant association between mercury levels and ADHD | Ha 2009 [42] |

MeHg – methylmercury; Pb – lead; Al – aluminum; ADHD – attention-deficit / hyperactivity disorder.

the dopaminergic neurons of the striatal-frontal circuitry. Among the psychological functions related to these circuits, there are response suppression and response variability [49,50].

Eleven studies evaluating the impact of lead exposure on ADHD or ADHD-related symptoms have been identified since 2000 (Table 4).

In the published studies, the relationship with ADHD was reported even at the blood lead level well below the CDC's 10 μg/dl action level. For instance, the analysis from the National Health and Nutrition Examination Survey on 4704 children aged 4–15 years indicated the prevalence of parent-reported ADHD diagnosis or treatment four times higher among children with the blood lead level > 2.0 μg/dl, compared with those with the blood lead level < 0.8 μg/dl (OR = 4.1; 95% CI: 1.2–10.0) [6]. The later analysis conducted as part of the same survey (on 2588 children at 8–15 years of age) indicated that children who were exposed to prenatal tobacco and lead had greater risk of ADHD than it would be expected if the independent risk was multiplied (OR = 8.1; 95% CI: 3.5–18.7; tobacco – lead exposure interaction $p < 0.001$) [51].

Additionally, studies conducted in South Korea [42], China [52], India [53], and the US [54,55] also suggest a link between the blood lead level and the diagnosis or symptoms of ADHD. Four studies investigating the link between lead exposure and ADHD and/or ADHD-related symptoms were published in 2010 [41,56–58]. The strength of those studies lies in the adjustments for a number of potential confounders, but their weakness is that each of them depended on a single concurrent blood lead level, making it difficult to disentangle the effects of prenatal or earlier childhood levels from the current levels. The findings of the studies are consistent with earlier literature reports demonstrating increased risk of ADHD or ADHD-related symptoms in case of lead exposure.

To sum up, the presented studies indicated that low lead exposure levels (with mean levels below the CDC action level of 10 μg/dl) are associated with the increased risk of ADHD.

**Manganese and ADHD or ADHD-related symptoms**

Manganese (Mn) is a naturally occurring element that constitutes approximately 0.1% of the Earth's crust, and low levels of Mn in water, food, and air are ubiquitous [59]. Several authors have hypothesized that excessive amount of Mn could have detrimental effects on children's behavior patterns [59].

High exposure to airborne Mn has been associated with neurotoxic effects, with the worst cases displaying the extrapyramidal syndrome (manganism), characterized by gait dysfunction with a propensity to fall backward, postural instability, bradykinesia, rigidity, micrographia, masked facies, speech disturbances, and muscle tremors [60]. Lower levels of exposure may produce neurobehavioral deficits involving motor and cognitive functions, as well as psychological perturbations [61,62].

So far, only two studies have been carried out to examine the association between exposure to Mn and ADHD or ADHD-like symptoms and both suggested the presence of such relationship [63,59] (Table 5).

A case-control study by Farias et al. [63] found that children with ADHD of both the inattentive and ADHD-combined types had higher serum manganese levels compared with the controls, however the study did not control for potential confounders. Also, the study performed in Quebec reported a significant association between higher manganese levels in hair and drinking water and hyperactive behaviors in school children after controlling for sex, age and income [59].

**Summary of the study results**

ADHD is a complex disorder with great heterogenicity in the behavioral symptoms and affected brain functions and structures [2]. Although much research has been done on the impact of genetic, environmental, industrial and

**Table 4.** Exposure to lead and ADHD or ADHD-related symptoms

| Country | Study population | Type of study | Definition of exposure | Test used | Confounding factors | Results | References |
|---|---|---|---|---|---|---|---|
| The United States – National Health and Nutrition Examination Survey 1999–2002 and 2001–2004 | 4 704 children 4–15 years of age | Survey | BLLs | Parental report of diagnosis of ADHD and current stimulant medication use | Age, gender, race, ETS, preschool or child care attendance, health insurance, ferritin level | Higher BLL (> 2 μg/dl vs. < 0.8 μg/dl) was significantly associated with ADHD (OR= 4.1; 95% CI: 1.2–14.0). | Braun 2006 [6] |
| | 2 588 children 8–15 years of age | | | DSM-IV | Age, gender, race, ETS, income, preschool attendance, mother's age at children's birth, birth weight | Higher current BLL (>1.3 μg/dl vs. < 0.9 μg/dl) was significantly associated with ADHD (OR=2.3; 95% CI: 1.5–3.8). Compared with the children with neither exposure, children with both prenatal tobacco and third-tertile lead levels had greater risk of ADHD than it would be expected if the independent risk was multiplied (OR = 8.1; 95% CI: 3.5–18.7; tobacco-lead exposure interaction $p < 0.001$) | Froehlich 2009 [51] |
| The United States, other studies | | | | | | | |
| Detroit | 506 children at the age of 7 | Cohort | BLLs | Conners' Continuous Performance Test, Conners' Teacher Rating Scale, Achenbach Teacher Report Form, PROBS-14 | SES, alcohol, smoking and drug use, psychopathology, HOME, maternal IQ | Higher BLL was significantly associated with hyperactivity ($p < 0.01$), social and delinquent behavior problems ($p < 0.05$) and attention ($p < 0.01$), but not with impulsivity ($p > 0.1$) | Chiodo 2007 [54] |

| | | | | | | |
|---|---|---|---|---|---|---|
| Michigan | 150 children 8–17 years of age | Case-control | KSADS, parent and teacher rating scales (ADHD Rating Scale and Conners ADHD Rating Scale) | Age, gender, income | BLLwas significantly higher in ADHD-combined type than in non-ADHD control ($p < 0.05$) children; BLL was associated with the symptoms of hyperactivity-impulsivity, but not inattention-disorganization; effects of blood lead on hyperactivity-impulsivity were mediated by poor performance on the stop task | Nigg 2008 [55] |
| Michigan | 236 children 6–17 years of age | Case-control | KSADS, parent and teacher rating scales (ADHD Rating Scale and Conners ADHD Rating Scale) | Age, gender, blood hemoglobin level, household income, maternal smoking, IQ | BLL was associated with ADHD-combined type, but not inattentive type; teacher's report showed effects on DSM-IV inattention symptoms. BLL was associated with hyperactivity-impulsivity in parent's report regardless of the measurement method ($p \leq 0.001$), whereas teacher's report effects depended on the child treatment history | Nigg 2010 [56] |

**Table 4.** Exposure to lead and ADHD or ADHD-related symptoms – cont.

| Country | Study population | Type of study | Definition of exposure | Test used | Confounding factors | Results | References |
|---|---|---|---|---|---|---|---|
| South Korea – Children's Health and Environment Research Survey | 1 778 children at 10 elementary schools | Survey | BLLs | The Korean version of the abbreviated Conners' scale for ADHD symptom screening | Age, gender, household income, parental history of neuropsychiatric diseases, residential area, blood mercury level | The risk for ADHD symptoms was found to increase with BLL (OR = 1.3; 95% CI 0.6–2.9 for 1–1.5 μg/dl; OR = 1.3; 95% CI: 0.6–2.7 for 1.5–2.5 μg/dl; OR = 1.7; 95% CI: 0.8–3.6 for 2.5–3.5 μg/dl and OR = 2.0; 95% CI 0.8–5.1, compared to those with BLL of < 1 μg/dl; p for trend: 0.07); BLL showed a significant positive association with the Conners' ADHD score (β = 0.5, p < 0.0001) | Ha 2009 [42] |
| | 256 children 8–10 years of age | Survey | | Teacher – ADHD Rating Scale, parents – Korean version of the Learning Disability Evaluation Scale, children – neurocognitive tests | SES, parental education, ETS, smoking during pregnancy, child gender | BLL was not significantly associated with the inattention scores (β = 1.8; 95% CI: –1.3–4.9), the hyperactivity subscores (β = 0.7; 95% CI: –2.1–3.5), and the total score (β = 2.5; 95% CI: –3.0–8.0); significant differences between the low (< 2.2 μg/dl) and high lead (> 2.2 μg/dl) groups with regard to inattention subscore (p < 0.01) and total score (p < 0.05). The probability of inattentive and hyperactive symptoms was increased with higher blood lead levels in boys with OR = 2.8 (p = 0.04) | Kim 2010 [58] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | 667 children 8–11 years of age | Survey | BLLs | Korean version of the ADHD Rating Scales (K-ARS) | Age, gender, educational level of the father, maternal IQ, child's IQ, residential area, birth weight, urinary cotinine | The inattentive, hyperactive and total scores of the teacher-related K-ARS were positively associated with BLL ($\beta = 0.16$; $p = 0.001$; $\beta = 0.19$; $p < 0.001$; $\beta = 0.18$; $p < 0.001$, respectively) | Cho 2010 [57] |
| China | 630 subjects with ADHD, 630 controls, all 4–12 years of age | Survey | BLLs | DSM-IV | Cases to controls matched on age, gender, SES; additional confounders: family history of ADHD, household composition, maternal tobacco and alcohol use during pregnancy, labor complications, cesarean delivery, perinatal distress, low birth weight and admission to a neonatal intensive care, parents' age at childbirth, and parents' education | ADHD cases were more likely to have been exposed to lead during childhood than the non-ADHD control subjects (children with BLL ≥ 10 μg/dl vs. ≤ 5 μg/dl; OR = 6.0, $p < 0.01$; 5–10 μg/dl vs. ≤ 5 μg/dl, OR = 4.9, $p < 0.01$) | Wang 2008 [52] |
| India, Chennai | 756 children, 3–7 years of age | Survey | BLLs | Conners' Teacher Rating Scales-39, Conners' ADHD/ DSM-IV Scales, Behavior Rating Inventory of Executive Function questionnaires | age, gender, hemoglobin, income, education, number of other children, clustering at school and classroom level | BLL was associated with higher anxiety ($\beta = 0.3$, $p = 0.01$), social problems ($\beta = 0.2$, $p = 0.02$), and higher scores in the ADHD index ($\beta = 0.2$, $p = 0.05$) | Roy 2009 [53] |

**Table 4.** Exposure to lead and ADHD or ADHD-related symptoms – cont.

| Country | Study population | Type of study | Definition of exposure | Test used | Confounding factors | Results | References |
|---|---|---|---|---|---|---|---|
| Romania | 83 children, 8–12 years of age | Survey | BLLs | German "Testbatteriezur Aufmerksamkeitsprüfung für Kinder–KITAP" (Test battery for attention performance of children) Behavioral Rating Scales | Age, gender, computer experience, handedness, eye problems, number of siblings, parental education, smoking/ alcohol use in pregnancy, family psychopathology, study area | Increasing BLL had borderline or significant associations with a parent's rating of hyperactivity ($t = 2.4$, $p = 0.02$) impulsivity ($t = 2.4$, $p = 0.02$) and ADHD total score ($t = 2.0$, $p = 0.05$) and teacher's ratings of impulsivity ($t = 2.2$, $p = 0.03$) | Nicolescu 2010 [41] |

DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; KSADS – Kiddie Schedule for Affective Disorders and Schizophremia; SES – socioeconomic status; HOME – Home Observation for Measurement of the Environment; BLLs – blood lead levels; ETS – environmental tobacco smoke exposure; β – coefficient.

**Table 5.** Exposure to manganese and ADHD or ADHD-related symptoms

| Country | Study population | Type of study | Definition of exposure | Test used | Confounding factors | Results | References |
|---|---|---|---|---|---|---|---|
| Brazil | 166 children attending public schools | Case-control | Serum concentrations of Mn in children | ADHD diagnosed by the doctor | No confounders | Children with ADHD had higher serum Mn levels compared with controls | Farias 2010 [63] |
| Canada, Quebec | 46 children aged 6–15 years | Cross-sectional | Mn in children's hair and public water system. | Revised Conners' Teachers Rating Scale (CTRS-R) and Revised Conners' Parents Rating Scale (CPRS-R) | Age, sex, income | Mn in hair was significantly associated with scores on the Oppositional ($p = 0.020$) and Hyperactivity ($p = 0.002$) subscales | Bouchard 2007 [59] |

Mn – manganese.

lifestyle factors on ADHD, we are still far from understanding its etiology. Given the inability to explain ADHD on a solely genetic basis, interest in the contribution of environmental/lifestyle factors, including exposure to industrial chemicals, has been intensified.

Table 6 presents the summary of the results of the studies analyzing the association between the exposure to industrial chemicals and ADHD or ADHD-like symptoms. Most of the presented studies are focused on pesticides, PCB and lead, whereas the impact of mercury and manganese has been investigated less frequently. The findings of the reviewed studies indicate that children's exposure to organophosphate pesticides may cause symptoms consistent with PDD as well as with ADHD or attention problems. Exposures to organochlorine pesticides and PCBs were associated with ADHD-like behaviors: alertness, quality of alert responsiveness, cost of attention, and other potential attention-associated measures including self-quieting and motor maturity. Lead is probably the best studied toxic element. The studies in this field provided evidence that low levels of lead in the blood (well below the CDC's 10 μg/dl action level) were associated with ADHD or ADHD-related symptoms and no threshold below which lead does not cause neurodevelopmental toxicity can be defended. Information from the studies on the association between mercury exposure, especially in the postnatal period, and neurotoxicity is limited. Therefore, the association between exposure to this heavy metal and ADHD requires further confirmation in future studies. Two studies indicated that there is an association between exposure to manganese and ADHD or ADHD-related symptoms. As there are no other studies on this topic, such exposure and its impact on child neurodevelopment need to be further investigated.

In the presented studies, the assessment of the exposure to industrial chemicals is based on the measurements of biomarkers and not questionnaire data, which decreases the risk of exposure misclassification. A single measurement during pregnancy, delivery or childhood period may not be sufficient to judge when the window of exposure occurred.

In some of the studies included in the review, ADHD diagnosis was made through an extensive clinical evaluation based on the DSM-IV diagnostic instrument. Others focused on specific symptoms – such as attention problems, impulsivity or hyperactivity.

The possible co-exposures to other relevant, but not measured, environmental/lifestyle contaminants and confounding factors are important issues to be considered in order to avoid under- or over-estimation of the association between the exposure and outcome of interest. For example, the analysis performed by Froehlich et al. [51] indicated that, compared with children with neither exposure, children with both exposures (prenatal tobacco and lead) had a greater risk of ADHD than would be expected if the independent risks were multiplied (tobacco-lead exposure interaction $p < 0.001$). Particularly important confounders include, parental intelligence, parental criminality and mental disorders to account for genetic background. For practical reasons, in some studies, maternal education/IQ and psychopathology are taken as proxy for the parental one. In addition to the heritability factors, the reported environmental risk factors for ADHD include: pregnancy and delivery complications, low birth weight, maternal smoking, and illicit drug and alcohol intake during pregnancy [42]. Furthermore, the quality of home environment (e.g. low social class, low income, large family size, family dysfunction and single parent families) has been reported to be a risk factor for psychopathology and behavioral problems in children. The quality of home environment is mostly measured by means of the Home Observation for Measurement of the Environment (HOME) Scale. It covers the emotional and verbal responsibility of the mother, acceptance of the child's behavior, organization of the home environment, availability of toys, parental involvement and variability of daily experience.

**Table 6.** Summary of chemical exposure impact on ADHD or ADHD-related symptoms based on the reviewed literature

| ADHD or ADHD-related symptoms | OP pesticides | PCB | Organochorine pesticides and PCB | Hg | Pb | Mn |
|---|---|---|---|---|---|---|
| ADHD | + Marks 2010 [20], Bouchard 2010 [19], Rauh 2006 [17] | – Lee 2006 [35] | + Sagiv 2010 [36] | + Cheuk 2006 [37] –Nicolescu 2010 [41], Ha 2009 [42] | + Braun 2006 [6], Wang 2008 [52], Froehlich 2009 [51], Nigg 2008 [55], 2010 [56], Ha 2009 [42], Roy 2009 [53] | + Farias 2010 [63] |
| Attention problems | + Marks 2010 [20], Sanchez-Lizzardi 2008 [21], Rauh 2006 [17] | + Grandjean 2001 [34] | + Sagiv 2008 [25] | + Juvlez 2010 [44] | + Chiodo 2007 [54], Cho 2010 [57], Kim 2010 [58] – Nigg 2008 [55] | |
| Impulsivity | | + Stewart 2003 [31], 2005[32], 2006 [33] | | | + Nigg 2008 [55], Nicolescu 2010 [41] –Chiodo 2007 [54] | |
| Hyperactivity | | | | + Myers 2003 [45] | + Chiodo 2007 [54], Nigg 2008 [55], Cho 2010 [57], Nicolescu 2010 [41] | + Bouchard 2007 [59] |
| Anxious and depressed behavior | | | | | + Roy 2009 [53] | |
| Delinquent behavior | | | | | + Chiodo 2007 [54] | |
| Pervasive developmental disorders | + Eskanzai 2007 [18], Rauh 2006 [17] | | | | | |
| Quality of alertness | | | + Sagiv 2008 [25] | | | |
| Longer response time; more variation in response time; impairment of response inhibition; impulsive responding | | + Verugdenhil 2004 [29] Stewart 2003, 2005, 2006 [31–33] | | | | |
| Worse working memory and concentration, orientation | | + Jacobson 2003 [30] | | | | |
| Deficits reaction time | | | | + Debes 2006 [43] | | |

"+" – statistically significant association between the exposure to environmental toxicants and ADHD or ADHD-related symptoms.
"–" – no statistically significant association between the exposure to environmental toxicants and ADHD or ADHD-related symptoms.

Finally, there is relatively extensive body of literature reporting the effects of neurodevelopmental exposure to pesticides, PCBs and lead. The impact of mercury and manganese on ADHD and ADHD-related symptoms needs to be further investigated. Future studies should use a prospective design, with multiple biological samples collected over time for the better assessment of exposure and its critical windows. Additionally, the inclusion of potential confounding factors and co-exposures is crucial for reliable assessment of the impact of exposure on ADHD.

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