Journal of Environmental Immunology and Toxicology 1:2, 92-104; May/June 2013; © 2013 STM Publishing

Environmental Chemical Contributions to ADHD and the Externalising Disorders of Childhood – A Review of Epidemiological Evidence

Christos Symeonides[1,2,3], Anne-Louise Ponsonby[1,3], Peter Vuillermin[1,2,3,4], Vicki Anderson[1,3,5], Peter Sly[6]

[1]Murdoch Childrens Research Institute, Melbourne, Australia; [2]Child Health Research Unit Barwon Health, Geelong, Australia; [3]University of Melbourne, Melbourne, Australia; [4]Deakin University, Melbourne, Australia; [5]Royal Childrens Hospital, Melbourne, Australia ; [6]Children's Health and Environment Program, Queensland Children's Medical Research Institute, the University of Queensland, Queensland, Australia

Abstract

The externalising disorders of childhood, Attention Deficit Hyperactivity Disorder (ADHD), Conduct Disorder and Oppositional Defiant Disorder are leading causes of childhood morbidity. Aetiology is poorly understood but includes both genetic and environmental factors. Here we review the observational evidence for an association between environmental chemical exposures and increased externalising behaviour in childhood. With respect to ADHD, we additionally consider whether there is evidence that exposures are associated with impairments in information processing skills characteristic of ADHD. We conclude that large, well designed, prospective studies combining behavioural and cognitive outcomes now provide strong evidence for an association between environmental lead exposure and the externalising disorders of childhood, as well as evidence for an association between prenatal exposure to environmental methylmercury and difficulties associated with ADHD. Existing epidemiological research on polychlorinated biphenyls is however inconclusive and we discuss evidence that the association between environmental tobacco smoke and externalising disorders may not be causal in nature. Finally modern environmental chemicals are reviewed where early studies have observed an association between increased exposure and externalising disorders, externalising behaviours, or information processing difficulties associated with ADHD, but where further replication is required. Implications for future research are discussed.

Journal of Environmental Immunology and Toxicology 2013; 1:92-104

Key words

environmental pollutants; lead; methylmercury compounds; polychlorinated biphenyls; attention deficit and disruptive behavior disorders; executive function; child; adolescent.

Introduction

The externalising disorders of childhood – comprising of Attention Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) – are important causes of childhood morbidity with substantial implications for later adult productivity, both through persistence of symptoms, and social and educational disadvantage. ADHD alone is estimated to be associated with an annual cost of 143-266 billion dollars to the US economy.[1] The prevalence of ADHD in the US has risen by around 33% over the last decade[2] and in Australia it is now the single most common reason for seeing a paediatrician, both initially and on review.[3] This temporal increase in incidence is too rapid to reflect genetic factors only, however the changes in the modern social and biological environment that account for this rising incidence are not known.

Correspondence to: Christos Symeonides, Murdoch Childrens Research Institute, Melbourne, Australia; Email: christos.symeonides@mcri.edu.au
Submitted: 28/01/2013; Revised: 15/03/2013; Accepted: 18/03/2013
DOI: 10.7178/jeit.21

Here we review the epidemiological evidence that environmental chemicals contribute to the incidence of ADHD, ODD and CD through neurodevelopmental toxicity. First, we will briefly outline the clinical disorders and the approaches used to study these disorders in observational research. This is followed by a discussion of the existing literature, starting with the environmental chemicals exposures which have been most extensively researched: lead, polychlorinated biphenyls (PCBs), methylmercury (MeHg) and environmental tobacco smoke (ETS). Subsequently, we review the expanding list of modern chemicals where environmental exposure has been observed to be associated with externalising behaviours in early studies, but where further validation is required (**Table 1**). As an example of this emerging literature, we discuss in detail the existing findings relating to bisphenol A (BPA) and phthalates. The scope of the review does not include mechanistic evidence.

Studying the externalising disorders of childhood in epidemiological research

Oppositional Defiant Disorder (ODD), Conduct Disorder (CD) and Attention Deficit Hyperactivity Disorder (ADHD)

are defined and diagnosed by behavioural criteria, set out in the Diagnostic and Statistical Manual of Mental Disorders published by the American Psychiatric Association (DSM IV).[4] ODD and CD are closely-related disorders[5] characterised by hostile and antisocial behaviours.[4] ADHD is defined in three subtypes by inattention, by hyperactivity and impulsivity, or by a combination of these. Similar clinical entities are defined in the World Health Organization's International Statistical Classification of Disease (ICD-10),[6] although less widely used. The underlying genetics and neurobiology are poorly understood, and although there is a greater understanding of ADHD than other externalising disorders, there are no clinically useful biomarkers.[7]

DSM-IV diagnostic criteria are common behavioural outcomes in epidemiological research, especially in case-control studies where an adequate number of cases can be anticipated. In population cohorts, where only a small proportion of individuals will meet clinical criteria, an alternative approach employs a continuous behavioural outcome. This increases the statistical power of the study, but relies on two assumptions: (i) that externalising behaviours exist on a unimodal continuum across the population; and (ii) that the same causal factors are relevant across that continuum. The continuum model is supported by evidence of complex polygenic inheritance and subclinical deficits detectable in unaffected relatives.[8-10] Multiple quantitative scales exist, and are well validated, including: the Achenbach Child Behavior Checklist (CBCL);[11] the Strengths and Difficulties Questionnaire (SDQ);[12] the Conners' Rating Scales-Revised (CRS-R);[13] the Infant-Toddler Social and Emotional Assessment (ITSEA);[14] and the Behaviour Assessment System for Children (BASC).[15]

In the ADHD literature, where a profile of characteristic deficits in information processing skills has been elucidated,[10,16,17] neuropsychological assessment of these information processing skills provides an alternative means to identify and quantify subtle neurocognitive effects of chemical exposures. In this review we follow Barkley's influential model of (combined-type) ADHD in terms of impairment in sustained attention and underlying deficits in executive functions.[16] Heterogeneity in executive function deficits is recognised across individuals and cohorts with ADHD,[10,17] however those that are most consistently observed include: working memory, response inhibition, cognitive flexibility (set shifting), and planning.[10,17] Executive function deficits do not appear to be a feature of other externalising disorders in the absence of comorbid ADHD.[18] It should be noted that ADHD is defined on behavioural grounds and caution is required in making inferences about ADHD by extrapolation from observed deficits in information processing skills. Nevertheless, they are attractive as an objective measure to complement behavioural outcomes. A review of the neuropsychological assessments that may be used to assess each of these information processing skills is beyond the scope of this paper, and the reader is referred to recent reviews by Aguiar, Eubig & Schantz,[10] Mahone & Schneider[19] and Anderson & Reidy.[20]

Method

Relevant articles were retrieved by a systematic review of journals indexed by the National Institute of Health Medline database. The database was searched for primary epidemiological research articles relating to potential environmental toxicants and neurodevelopment in childhood, using MESH terms. Potential environmental toxicants were defined broadly to include relevant MESH terms for environmental pollutants, but also the broader chemical classes of known or suspected neurodevelopmental toxicants from previous reviews (e.g. halogenated organic compounds for PCBs, or metals for lead).[21-25] Neurodevelopment was also defined broadly to include studies where outcomes relevant to behavioural disorders might be included within broader studies of neurodevelopment. Full details of the search strategy are available on request from the primary author (CS). This search identified 1844 articles which were reviewed by the primary author in a 3 stage process, starting with titles (or their English translations), followed by abstracts. Papers with potentially relevant outcomes and exposures, or where no abstract was available, were then reviewed in full. Additional papers were identified from review of the reference lists of included papers. In restricting the scope to environmental exposure, high-dose exposure through medications, poisoning or illicit drug use were excluded. Similarly, environmental tobacco exposure was included but not maternal smoking during pregnancy.

Lead

Lead is an established developmental neurotoxicant. An association between low level environmental lead exposure and general cognitive development, raised by Needleman in 1979,[26] is now established,[27,28] with no safe level found in the most recent studies.[29,30] Prenatal,[30, 31] lifetime,[28,30-34] and concurrent lead levels[27,35] all appear to be important.[28,31,36]

Externalising behaviours

Cross-sectional studies have consistently reported associations between even low-level lead exposure and an increase in externalising behaviours, including hyperactivity-inattention difficulties,[37-40] aggression,[39,41] rule-breaking behaviours,[37,39,41] and total externalising behaviours;[39,42,43] as well as the clinical disorders of CD[44] & ADHD.[40,45,46] We identified five longitudinal cohorts which have studied potential windows of vulnerability through repeated sampling. Each did observe increased externalising behaviour with increased lead exposure but with differences regarding the relevant timing of exposure. Studies by Dietrich et al. in the US[47] and Wasserman et al. in the former Yugoslavia[48] have reported associations with both current and prenatal lead exposure, and indeed Wasserman et al. observed associations between destructive behaviours on the CBCL at 3 years and blood lead at all time-points from birth onwards.[48] However, the three remaining cohorts have observed association with the most recent lead measurement only,[49,50] most recently in a cohort of northern Quebec Inuit.[51,52] At 11 years, current but not cord blood lead was associated with increased externalising behaviours and a trend towards increased attention problems on teacher-report (CBCL).[52] This translated into an increase in those meeting DSM-IV criteria for ADHD-hyperactive-impulsive type in both the second and third tertiles of exposure (but not ADHD-inattention type, ODD or CD).[52] In the same cohort at 5 years, current but not prenatal

lead exposure had been associated with increased irritability, impulsivity and inattention.[51]

Information processing skills

Complementing observations of the association between increased lead exposure and the behaviours of ADHD, impairments in the information processing skills that characterise ADHD have also been evaluated across epidemiological studies. This literature has methodically reviewed and well tabulated by Eubig, Aguiar and Schantz in a recent systematic review,[21] to which we refer the reader and extend here. The most consistently observed associations identified in that review were impairments in cognitive flexibility and sustained attention; less consistently observed associations included impaired working memory, planning and response inhibition.[21] We identified six additional studies with relevant outcomes.[32,39,53-56] Notably, the findings of these studies do not conform well to the pattern of deficits previously described. In the two additional studies to assess cognitive flexibility, this was not associated with tooth dentine lead[56] nor bone lead,[39] and whilst impairment in sustained attention was further replicated by Nigg et al.[53] and Boucher et al.,[54] Kicinski et al. found no significant association with blood lead in their cross-sectional study of Flemish adolescents.[55] Findings for response inhibition followed those for sustained attention across those three studies. Finally impaired working memory (WISC Freedom from Distractibility composite) was found to be associated with increased lifetime lead exposure in the Yugoslavia Prospective Study at 7 years of age,[32] but no association between blood lead and working memory (backward digit recall) was observed in the Flemish cohort.[55]

Summary

In conclusion, there is well replicated evidence for an association between lead exposure, even at very low levels, and the externalising behaviours of ADHD, CD and ODD, and evidence that this does translate into increased odds of ADHD and CD. There is complementary evidence that lead exposure is associated with impairments in specific information processing skills relevant to ADHD, although no consistent pattern of deficits is established. Whilst the strongest evidence is for current lead exposure, prenatal and lifetime lead exposure may also be important, as is the case with general cognitive outcomes.

Polychlorinated biphenyls (PCBs)

PCBs are a group of synthetic organochloride chemicals that were used widely in the 1970s as coolants and lubricants in electrical equipment.[57] They persist in the environment today, and are recognised and regulated as Persistent Organic Pollutants within the Stockholm Convention.[58] Human exposure through older electrical equipment continues, although diet is another important source. PCBs bioaccumulate through the food chain, and fish from contaminated freshwater areas and marine animals are important sources.[57]

Externalising behaviours

Neurodevelopmental toxicity of the polychlorinated biphenyls was first observed in studies of a Taiwanese cohort - the Yu-Cheng cohort - born in a 6 year period from 1979-1985 after their mothers were exposed to high levels of PCBs in contaminated cooking oil.[59] In a matched special exposure cohort study design, children born following this exposure had lower general cognitive performance, and greater behavioural difficulties as measured through parent report on the CBCL and Rutter Child Behaviour scale, as well as greater hyperactivity on the Werry-Weiss-Peters Activity scale.[60] Many subsequent studies have investigated neurodevelopmental toxicity due to prenatal environmental PCB exposure, but we only identified four cohorts that have considered an association between PCB and externalising behaviours or disorders, with inconclusive findings. In a cohort living near a PCB-contaminated harbour in New Bedford, Sagiv et al. observed increased ADHD-related behaviours on the CRS-R for Teachers at 7-11 years in association with the sum of 4 PCB cogeners in cord blood.[61] This finding was not replicated in the other studies, although none had such a large a sample size. Roze et al. did observe positive correlation between increased externalising behaviours on the CBCL at 6 years and maternal serum PCB during pregnancy in the Dutch COMPARE cohort, but the statistical evidence was weak ($p<0.10$).[62] A study of a northern Quebec Inuit cohort with increased PCB exposure through diet, did observe an association between increased PCB 153 in cord blood and irritability at 5 years,[51] however a broader assessment of the cohort at 11 years observed little evidence for an association between current or cord blood PCB 153 and teacher-reported attentional difficulties or total externalising behaviours on the CBCL, nor with the odds of meeting DSM-IV criteria for ADHD, CD or ODD.[52] Finally a Slovakian cohort, which has been published in abstract form only, found no association between subscale scores on the CBCL at 45 months and the sum of 6 PCB congeners in either maternal prenatal or child specimens.[63]

Information processing skills

Boucher et al.[64] and Eubig et al.[21] have each recently reviewed PCB exposure in relation to the neurocognitive deficits associated with ADHD. In the more recent of the two reviews, Eubig et al. describe a pattern of deficits that differs from the pattern that was reported for lead exposure: the most consistently replicated findings were impairment in working memory, response inhibition and cognitive flexibility associated with increasing prenatal PCB exposure, with less consistent findings of impaired sustained attention.[21] Extending the findings of that review, our search identified five additional cohorts with relevant outcomes, in cohorts from the Faroe Isles,[65,66] the US (New Bedford),[67] northern Quebec,[54] the Netherlands (COMPARE)[62] and Menorca, Spain.[68] These studies do not support previously observed associations with response inhibition, nor that with working memory, but do now provide replication of impaired attention across three different cohorts. No additional studies were identified that assessed cognitive flexibility, which has been found to be impaired across two tasks at 11 years of age, in association with prenatal PCB exposure in a Lake Michigan cohort.[69]

Working memory was assessed at 14 years of age in the Faroe Isles cohort, a community exposed to higher levels of PCBs through consumption of whale blubber (verbal and spatial span backwards);[66] as well as in the New Bedford cohort (WISC-III Freedom from Distractibility subscale at 8 years of age).[67] In

contrast to the findings in cohorts from Lake Michigan,[69] the Netherlands[70] and Oswego (New York),[71] neither replicated an observed association between increased prenatal PCB exposure and impaired working memory. Higher prenatal PCB exposure had also been consistently observed to be associated with errors of commission (impaired response inhibition) on a continuous performance test (CPT) in the Oswego[72,73] and Lake Michigan cohorts.[69] CPTs were however also administered in four of the additional cohorts we identified and none replicated those findings.[54,66-68] An association observed in the Faroe Island study between increased prenatal PCB exposure and an increase in missed responses on a CPT at 7 years of age (a common measure of impaired sustained attention),[65] is unlikely to be significant. This association has not been observed across any of the other cohorts to have included a CPT, nor in the same cohort when retested at 14 years.[66] More interesting, however, is an association between prenatal PCB exposure and impaired reaction time that is replicated across the New Bedford, northern Quebec and Spanish cohorts.[54,67,68] This CPT measure of attention is understood to tap a separate aspect of attention from missed responses,[21] and is also associated with ADHD, albeit less strongly.[10]

Postnatal exposure

Although postnatal PCB exposure is associated with neurodevelopmental toxicity in animal studies,[74] there is little evidence for this in human observational studies to date. Postnatal exposure to PCBs has been studied in four major longitudinal cohorts: Lake Michigan,[75] Rotterdam,[76] northern Quebec[51] and Germany,[77] but only the latter observed an association between increased postnatal exposure and neurodevelopmental harm, specifically poorer performance on the Bailey Scales of Infant Development at 30 months and Kaufman Assessment Battery for Children at 42 months.[77] Externalising behaviours and relevant information processing skills were not studied in this cohort. Relevant information processing skills were assessed in each of the other studies, with little evidence of an association with postnatal PCB exposure. The Rotterdam cohort observed weak evidence of an association between impaired planning (Tower of London task) at 9 years and higher early postnatal exposure through breast milk.[78] No other associations have been observed between any measure of postnatal exposure and any relevant information processing skills across the cohorts including: planning (Rey Complex Figure) and sustained attention (Simple Reaction Time Test) at 9 years in the Rotterdam cohort;[78] working memory (WISC Freedom from Distractibility composite) at 11 years in the Michigan Lake cohort;[79] attention at 4-5 years,[51] and sustained attention and response inhibition (go/no-go task) at 11 years in the Quebec cohort.[54] We identified one cross-sectional study to explore postnatal PCB exposure. In a cohort of adolescents in Belgium, Kicinski et al. observed an association between higher concurrent blood PCB and impaired sustained attention on a CPT, but no association with response inhibition, or with working memory on a backwards digit recall task.[55] Due to the study design it is impossible to exclude confounding by prenatal PCB exposure.

We found three studies to investigate the association between increased postnatal PCB exposure and externalising behaviours, with null findings in each. Jacobson et al. observed higher postnatal PCB to be associated with decreased activity on a complex, composite measure at 4 years,[75] whilst no association was observed with activity in the northern Quebec cohort at 4-5 years,[51] nor with externalising behaviours in a broad evaluation at 9-14 years.[52] Finally the prospective association between current PCB 126 and ADHD was considered in the NHANES 1999-2000 cohort with null findings, although confidence intervals were wide.[80]

Summary

In conclusion, evidence for an association between PCB exposure and externalising behaviours is restricted to prenatal PCB exposure and ADHD-related behaviours, and based upon a single study which has not been adequately replicated. There is no evidence to support an association with the behavioural difficulties of CD or ODD, other than in incidents of poisoning. Further evaluation of these findings is limited by the paucity of studies with relevant outcomes, and small sample sizes. By contrast, multiple studies of prenatal PCB exposure have reported on relevant information processing outcomes. As with lead, a consistent pattern of deficits has not emerged, but deficits are frequently observed across a range of information processing skills relevant to ADHD.

A better understanding of the underlying biology may be necessary to resolve the significance of contrary findings in the association between PCB exposure and difficulties associated with ADHD. Comparison of studies is challenging due to differences in categorising exposure. The PCBs include 209 congeners with differing chemical properties. Schantz et al.[81] have argued for a need to move towards congener-specific (or congener group-specific) studies, an approach taken for example by Park[82] and Newman[83] with respect to global cognitive development, but the challenges are substantial. There is considerable covariance between congeners, and with other persistent organic pollutants such as dioxins;[70,78] and given the large number of congeners detected, as well as uncertainty as regards the underlying biological pathway, it is unclear how to define biologically relevant groups of congeners, or to estimate relative potencies within groups.

Methylmercury (MeHg)

MeHg has established developmental neurotoxicity in humans,[84] the history of which has recently been reviewed by Grandjean et al.[85] Although neurotoxicity due to high dose mercury poisoning was well established, the evidence for neurodevelopmental toxicity due to environmental exposure has been controversial until very recently. Conflicting findings were observed in the three early cohorts from New Zealand, the Seychelles and the Faroe Isles. In the Seychelles cohort, with dietary mercury exposure from ocean fish, no consistent associations were observed over 17 years of follow-up, after accounting for the large number of endpoints evaluated.[86] By contrast, multiple negative associations with diverse neurodevelopmental outcomes were observed in a Faroe Isles cohort with similar exposure levels though a diet that included sea mammals.[66] The New Zealand data[87] had supported the findings in the Faroe Isles; and of the five subsequent longitudinal cohorts that have addressed the issue, four have now demonstrated association between higher prenatal MeHg exposure and poorer cognitive and psychomotor outcomes in early childhood, all within typical

levels of exposure.[88-91] The one exception being a large Spanish cohort in which the association was only observed within the girls in the study.[92] Recent work, including a new Seychelles cohort,[93] suggests that differences in the findings of the early studies may have been due to co-exposure to beneficial nutrients in seafood[88,94] specifically long-chain polyunsaturated fatty acids (LCPUFAs)[93,95] and observed benefits of fish consumption do appear to vary by type of fish consumed.[94]

Externalising behaviours

Externalising behaviours were considered within the Seychelles cohort, but not in the Faroe Isles. The Seychelles study included the Infant Behavior Scale of the Bayley Scales of Infant Development (IBS) at 29 months, the CBCL parent report form at 66 months[96,97] and 9 years,[98] the CRS-R Teachers hyperactivity index at 9 years,[98] and self-report of problematic behaviours at 17 years.[86] Consistent with other neurodevelopmental findings in this cohort, no association was found between MeHg exposure through fish consumption and parent reported or self-reported behaviours, although analysis of the CBCL subscales at 9 years does not appear to have been published. An individual, third-party reported measure – referral to a school counsellor for problematic behaviour - was associated with increased prenatal MeHg exposure,[86] but the significance of this is unclear. Interestingly, a decrease in the teacher-reported CRS-R hyperactivity index was observed at 9 years in association with increased MeHg exposure, and this concurs with an observation of reduced activity on the IBS at 29 months, but further analysis suggested that it was likely to be a spurious result due to multiple endpoints.[98] The possible benefits of fish-derived nutrients such at LCPUFAs were again not assessed nor controlled for.

Three subsequent cohorts have now considered externalising behaviours in environmental MeHg exposure. Cao et al. found no association between postnatal blood MeHg (2 years of age) and parent-reported behaviour at 5 years (CRS-R), nor parent-reported and teacher-reported behaviour at 7 years (BASC), although it should be noted that this cohort additionally had a history of high lead exposure.[99] Boucher et al. have studied both pre- and postnatal MeHg exposure in their north Quebec Inuit cohort. At 11 years, higher pre- but not postnatal MeHg exposure was associated with increased attention problems on the teacher-reported CBCL, and a trend towards increased externalising problems.[52] This was reflected in an increase in the proportion with attention problems and hyperactive/impulsive problems in the clinical range for the highest tertile of exposure versus the lowest. Little evidence was observed for an association with ODD or CD. Finally, Sagiv et al. observed an association between prenatal (but not postnatal) MeHg exposure and teacher-reported inattentive and hyperactive/impulsive behaviours (CRS-R) at 8 years in a New Bedford cohort, controlling for maternal fish consumption.[88] Interestingly fish consumption was independently associated with reduced symptoms, confirming the importance of controlling for this potential confounder. Behavioural outcomes in the second Seychelles cohort, which also controls for maternal nutrition and fish consumption, have not yet been reported.

Information processing skills

The batteries of tests for the Faroe Isles cohort and first Seychelles cohort each included assessment of information processing skills that are commonly impaired in ADHD. Again consistent with their wider findings, the Seychelles study did not observe any associations with MeHg exposure and any outcome, including: the A not B and "delayed spatial alternation" tasks (measures of working memory and inhibition, more typically used under 12 months[100]); recategorised "attention" and "executive function" subscales derived from the McCarthy Scales at 66 months;[96,101] inhibition and sustained attention on a CPT at 9 years of age;[98] spatial working memory and cognitive flexibility on the Wisconsin Card Sorting Test and CANTAB test battery at 17 years.[86] Analysis of the subscale performance on the WISC III at 9 years does not appear to have been published.

By contrast, and again in concurrence with their wider findings, Grandjean et al. observed that higher prenatal (but not postnatal[102]) MeHg exposure was associated with both more missed responses (poorer sustained attention) and longer average reaction time on the CPT at 7 years in the Faroe Isles cohort.[103] This association persisted after controlling for prenatal PCB exposure.[65] In a more extensive battery at 14 years, a CPT was used that assessed response inhibition (errors of commission) in addition to sustained attention (missed responses).[66] The association between prenatal MeHg and CPT reaction time was replicated, but no association was observed with missed responses, or with response inhibition. An association was however observed between higher prenatal MeHg exposure and reduced cognitive flexibility on the Children's Category Test. Equivocal findings were observed for working memory, with MeHg associated with spatial but not verbal span tasks that may have not been specific to working memory, tapping both short-term memory (forward recall) and working memory (backwards recall). Average maternal fish consumption was recorded but not controlled for in analysis of these specific information processing tasks.

Findings from subsequent cohorts have not resolved these contrasting findings, but do hint that fish consumption may confound the association between MeHg and these information processing tasks, just as it does for general IQ and ADHD-related behaviours. Cohorts from northern Quebec, Oswego (New York) and a US study of lead-exposed children, have evaluated performance in relevant information processing tasks, but without controlling for fish intake. In the northern Quebec cohort, no evidence was found for an association between either pre- or postnatal MeHg and observed attention or activity at 5 years,[51] nor with response inhibition (errors of commission in a go/no-go task) or sustained attention (missed responses) at 11 years, after controlling for confounders.[54] Both pre- and postnatal MeHg did however appear to be associated with reaction time, an alternative measure of attention.[54] The New York Oswego cohort observed prenatal MeHg to be associated with poorer performance in working memory at 9 years (WISC Freedom from Distractibility composite),[71] as well as a measure of response inhibition at 9.5 years (Differential Reinforcement of Low Rate task.[104] No association was observed with response inhibition in a CPT, assessed at 4.5,[72] 8 and 9.5 years.[73] Reaction time and missed responses (sustained attention) on the CPT were not analysed, and attention or

executive function subscales were not derived from the McCarthy Scales at 54 months[105] as others have done.[101,106] Finally, Cao et al. found no association between blood MeHg at 2 years and CPT performance at 7 years, nor any item of the NEPSY at 5 or 7 years, in a cohort with high lead exposure.[99]

Two studies have accounted for fish intake. In the Grenada INMA cohort, the only relevant outcome was an Executive Function subscale derived[106] from the McCarthy Scales.[94] No association was observed with current hair MeHg.[94] In a New Bedford cohort, Sagiv et al. observed higher prenatal MeHg to be associated with a small increase in errors of commission on the CPT, but only weak evidence to support a trend towards poorer performance in the WISC Freedom from Distractibility (working memory) composite.

Summary

To summarise, the evaluation of neurodevelopmental toxicity associated with MeHg exposure has been complicated by apparent benefits of fish intake. Controlling for this, there is evidence for an association between higher prenatal MeHg exposure and subsequent inattention, hyperactivity and impulsivity, which appears to be restricted to prenatal exposure. Wider externalising problems have not been adequately studied. Information processing impairments associated with ADHD have been observed across multiple studies but must be considered inconclusive at present. Future studies that account better for co-exposure to both persistent organic pollutants and the nutritional benefits of fish consumption may help to clarify inconsistencies in the pattern of specific cognitive deficits observed.

Environmental tobacco smoke (ETS)

There is a well-established association between maternal smoking during pregnancy and adverse neurodevelopmental outcomes, including symptoms of attention deficit and hyperactivity[107] and diagnosis of ADHD[45] and CD.[44] Further to this, correlations between ETS and adverse neurodevelopmental outcomes have been repeatedly observed, both in terms of maternal exposure during pregnancy and postnatal exposure of the child.[108-112]

A number of recent studies with very different methodologies have, however, raised doubts about whether the observed associations are causal in nature, or reflect, in part, shared genetic susceptibility. Langley et al.[113], analysing data from the large UK-based Avon Longitudinal Study, have reported that with respect to the odds of ADHD at 7-8 years, the effect size for paternal smoking during pregnancy was of similar magnitude to those for maternal smoking. No increased odds were observed for maternal exposure to other sources of environmental tobacco smoke (in the subset where neither parent smoked). The same group had previously shown that, in a cohort of children born following assisted reproduction technique, the magnitude of association between smoking during pregnancy and ADHD symptoms was greater in those where the mother was genetically related.[114] Indeed, no statistical increase was observed for children who were genetically unrelated (i.e. where a donor ovum was implanted, or where a surrogate was used). In a third approach, Maughan et al. used a twin study to explore the relative contribution of genetics to an observed association between prenatal smoking and childhood conduct problems, supported by detailed data of lifetime antisocial behaviour in the parents.[115] Controlling for this, genetics, and for socio-demographic factors, no statistically significant residual association persisted between prenatal smoking and childhood conduct problems.[115]

The implications of each of these studies would be equally relevant for observed associations between externalising behaviour and ETS exposure. Studies have not generally distinguished ETS from non-relatives to ETS from the father and other relatives, so shared genetic risk may again be an alternative explanation for observed associations.

Other work has however implied that the observed association between tobacco exposure and externalising behaviour cannot be fully accounted for by the shared genetic susceptibility of parental smoking and childhood externalising behaviours. In contrast to the findings at 7-8 years-old, analysis of 4 year-old outcomes in the same Avon Longitudinal Study cohort did report substantially different effect sizes for paternal and maternal smoking,[112] as have others,[108] and neither Thapar et al. nor Maugham et al. were adequately powered to exclude a substantial independent effect of maternal smoking. Indeed, by considering detailed lifetime history of parental antisocial behaviour, Buschgens et al. have observed a residual independent association between maternal smoking during pregnancy and externalising behaviours at 10-12 years, although they did not report on ETS separately.[116]

This uncertainty may be resolved in future larger twin cohorts, or by improved methodologies for quantifying parental neurodevelopmental histories - and thus genetic risk - within population cohorts. An alternative approach would be to more explicitly investigate the proposed biological pathways in parallel with the outcome. Thus Hsieh et al. have found support for a causal association between maternal ETS and neurodevelopmental outcomes, by considering genetic susceptibility to ETS, and looking for effect modification by polymorphisms genes that code for enzymes on relevant metabolic pathways.[110,117]

Other environmental chemicals

Human exposure to lead, PCBs, MeHg and ETS cannot account for the increasing prevalence of neurodevelopmental disorders observed in developed countries over recent years. Exposure to lead,[118] PCBs[119,120] and tobacco[121] is in decline, and although we could not find reliable data on temporal trends in MeHg in human tissue, there has been little change in total mercury concentration in human blood from successive NHANES cohorts in the US.[122] There is therefore substantial interest in other modern chemicals.[22] **Table 1** lists chemicals where at least one cohort has now observed an association between exposure and either externalising disorders, externalising behaviours or impairment in information processing skills relevant to ADHD. Many of these are known or suspected "endocrine disrupting chemicals" – chemicals which like PCBs interact with endocrine function.[123] Important methodological issues raised by endocrine disruption as a potential mechanism of developmental neurotoxicity include the potential for differential effects by gender, and non-monotonic effects with harm at low concentrations that cannot be predicted from effects at higher

doses.[124] Here we review the existing data on bisphenol A (BPA) and on phthalates as examples of this research.

Bisphenol A

BPA is a ubiquitous chemical used as an additive in many plastics, and in the production of polycarbonate plastics and epoxy linings. Other uses include in dental resins and thermal printing. The main source of human exposure appears to be through food and drink containers.[125-127] The link between prenatal BPA exposure and externalising behaviours in childhood has now been studied in 2 cohorts,[128,129] both in the US, and each with typical population levels of exposure.[128,129] Each observed a gender-specific association, but with contrary findings. In the Ohio HOME cohort[128,130] increased externalising behaviours were observed for girls at 2 years, and specifically increased hyperactivity (c.f. aggression or inattention) at 3 years, both on the parent-reported BASC.[123,125] The estimated effect size was substantial (an increase in symptoms equivalent to the population standard deviation, for each ten-fold increase in BPA). Although executive functions were not assessed directly, poorer performance on a parent-reported measure (the BRIEF) supported the findings on the BASC. The association for boys was in the opposite direction, however these were less substantial and p-values were only reported for the interaction with gender. In the New York CCCEH cohort, higher prenatal BPA exposure was observed to be associated with increased externalising behaviours (aggression) at 3-5 years in the boys (p=0.003) with the opposite seen in girls, although evidence for statistical significance of the latter finding was borderline given the multiple outcomes considered (p=0.02).[129] Similar covariates were considered in both studies. A different parent-reported behavioural assessment was used (CBCL), and there were differences in the timing of the measures BPA exposure, but both studies also had wide confidence intervals and further replication will be required to interpret the significance of these findings. Prenatal BPA exposure has been studied in the Korean MOCEH cohort,[131] but behavioural outcomes have not been reported to-date. No studies have yet reported investigation of BPA and clinical diagnosis of ADHD or other externalising disorders, nor information processing skills impaired in ADHD.

Phthalates

Phthalates are a group of chemicals with a broad range of applications, most notably as plasticizers in soft plastics like PVC, and solvents in personal care products, paints and adhesives.[132] In a cross-sectional study of Korean schoolchildren a correlation was observed between current phthalate exposure with both ADHD behaviours and performance on a CPT.[133] No further studies of postnatal exposure have been published to investigate the temporal relationship between exposure and externalising behaviours, however the potential association between prenatal phthalate exposure and childhood externalising behaviours has now been explored in two longitudinal cohorts. Prenatal phthalate exposure was analysed alongside BPA exposure in the New York CCCEH cohort, with no association observed with externalising behaviours on the CBCL at 3 years, although evidence of neurodevelopmental toxicity in other domains was reported.[134] A second New York cohort (the Mount Sinai cohort) did however observe an association between low molecular weight phthalates and aggression, conduct problems and attention problems reported on the BASC at 4-9 years, with an estimated increase of 2.9, 3.9 and 3.0 in the respective T-scores for each 10-fold increase in total maternal urinary low molecular weight phthalate concentration.[135] Executive function was assessed on the parent-reported BRIEF with impairment observed that supported the findings on the BASC.[135] There were differences in the ages of the cohort, the behavioural scales used, and subtle differences in the set of phthalate metabolites tested, however the effect size detected in the Mount Sinai cohort was moderate given the wide confidence intervals of both studies, and it would be important to interrogate this in a larger cohort before drawing conclusions. The possibility of selection bias should also be considered, with only 47% of the original Mount Sinai cohort included in the analysis (c.f. 90% for the CCCEH cohort). It therefore remains now for their findings to be replicated. Prenatal phthalate exposure has been studied in the Ohio HOME cohort[136] and in the Korean MOCEH cohort.[137] However, although a behavioural assessment was certainly competed in the HOME cohort at both 2 and 3 years-old,[128,130] an analysis with prenatal phthalate exposure has not been published to-date. No studies have reported investigation for associations between phthalates and clinical diagnosis of ADHD or other externalising disorders, nor with information processing skills impaired in ADHD.

Conclusions

In conclusion, the majority of existing epidemiological research into environmental chemicals and the externalising disorders of childhood has focused on four exposures: lead, methylmercury, PCBs and ETS. Large, well designed, prospective studies combining behavioural and cognitive outcomes now provide strong observational evidence for an association between lead exposure, specifically current lead, and externalising disorders; however the relevance of other exposures remains less clear. There is consistent evidence that prenatal MeHg exposure is associated with the behaviours that characterise ADHD, if fish intake is controlled for, and this is supported in part by evidence of impairment in relevant information processing skills; however it is not yet established whether this translates into an increase in the odds of clinical ADHD. Prenatal exposure to PCBs is associated with impairment in information processing skills relevant to ADHD, but there is insufficient data on behavioural outcomes to infer the clinical significance of this. Finally, there is substantial uncertainty whether the well-established association between ETS and ADHD is causal in nature or due to shared genetic inheritance.

Early findings across a broad range of modern chemicals have now prioritised a new set of exposures for investigation, and this epidemiological work will benefit greatly from lessons learned from the research into lead, MeHg, PCBs and ETS. This has, for example, demonstrated the importance of large birth cohort studies, with sophisticated approaches to measuring outcomes and covariates across the lifespan. Such studies have improved the sensitivity to detect small effects sizes of substantial public health importance, and in addition the temporal association between

exposures and outcomes supports causality. Significantly, this research has also recognised key challenges of inferring causation from observed associations, the importance of replication, and demonstrated the importance and challenge of identifying and accounting for covariates. Replication across different populations has identified important potential confounding factors, and future studies should, for example, carefully measure and account for breastfeeding (as illustrated by the PCB literature), genetic risk (as illustrated by the ETS literature) and consider potential co-exposure with known neurotoxicants or nutritional factors, including LCPUFAs and fish consumption (as illustrated in the MeHg literature). The incorporation of multiple exposures and multiple outcomes within a cohort has proven useful, and is cost-effective, and although there are potential statistical issues with multiple analyses, these can be addressed. In the studies we have reviewed here, assessment of relevant information processing skills has complemented behavioural and clinical outcomes and has improved confidence in findings replicated across these modalities of outcome. It is hoped that opportunities for this may improve as better understanding of the externalising disorders leads to more specific cognitive or biological endophenotypes.

Finally, several recent reports have shown elegant extensions to their study design, evaluating the proposed biological pathway in parallel to the outcome. This approach has broad potential for observational studies of environmental toxicity. It has, for example, been applied to organophosphate pesticide exposure, considering gene variants in its metabolic pathway as effect modifiers for neurodevelopmental outcomes;[138,139] and nitrogen dioxide exposure, considering gene variants in antioxidant defences.[140] Nor is the approach limited to genetic variants that confer differential risk. A recent paper by Wise et al. has for example employed a similar strategy to explicitly assess thyroid hormone disruption as a pathway between prenatal PCB exposure and childhood IQ.[141] As the underlying biological pathways of developmental neurotoxicity are better understood, it will become increasingly possible to incorporate putative causal pathways into

Table 1. Chemicals where increased environmental exposure has been observed to be associated with increased externalising behaviours, with externalising disorders, or with information processing difficulties characteristic of ADHD

Chemical exposure	Details of exposure	Cohort	Findings
Bisphenol A	Prenatal	US (HOME; Ohio)	↑ Externalising behaviours (BASC) in girls but not boys at 2 (n=249)[130] & 3 years (n=239)[128] ↓ Reported executive function (BRIEF) in girls but not boys at 3 years (n=237)[128]
		US (CCCEH; NY)	↑ Externalising behaviours (CBCL) in boys but not girls at 3-5 years (n=198)[129]
Phthalates	Current	Korea	↑ ADHD-related behaviours (DSM-IV) at 8-11 years (n=261)[133] ↓ Sustained attention & response inhibition (CPT) at 8-11 years (n=261)[133]
	Prenatal	US (Mount Sinai; NY)	↑ Aggression, conduct problems and attention problems (BASC) at 4-9 years (n=149-161)[135] ↓ Reported executive function (BRIEF) at 4-9 years (n=171)[135]
		US (CCCEH; NY)	– Externalising behaviours (CBCL) at 3-5 years (n=277)[134]
Organochloride pesticides	Prenatal DDT	Spain (Menorca)	↓ Executive function & working memory (McCarthy Scales) at 4 years for those with the *GSTP1* genotype only (n=177 of 326)[140]
	Prenatal DDE	Spain (Menorca)	– Executive function & working memory (McCarthy Scales) at 4 years (n=326)[140] – Sustained attention, response inhibition, alertness (CPT) at 11 years (n<393)[68]
		US (Oswego; NY)	– Response inhibition at 8 (CPT; n=174)[73] & 9.5 years (CPT & DRL; n=183)[73,104] – Working memory (WISC-III Freedom from Distractibility) at 9 years (n=155)[71]
		US (New Bedford)	– ADHD behaviours (CRS-R) at 7-11 years (n=573)[61] – Sustained attention, response inhibition, alertness (CPT) at 7-11 years (n=578)[67] – Working memory (WISC-III Freedom from Distractibility) at 7-11 years (n=584)[67]
	Postnatal DDE (4 years)	Spain (Menorca)	↓ Alertness (CPT) at 11 years (n<393)[68] – Sustained attention, response inhibition (CPT) at 11 years (n<393)[68]
Organophosphate pesticides	Current	US (NAHNES; 2000-2004)	↑ ADHD (DISC-IV or ADHD medication) at 8-15 years (n=1139)[142]
		Ecuador	– Sustained attention, response inhibition, alertness (CPT) at 6-8 years (n=81)[143]
		Egypt (children applying pesticides)	↓ Working memory (WAIS) at 9-19 years (n=50)[144] ↓ Attention (WAIS) at 9-19 years (n=50)[144]

Table 1 continued.

Table 1. Chemicals where increased environmental exposure has been observed to be associated with increased externalising behaviours, with externalising disorders, or with information processing difficulties characteristic of ADHD (continued)

Chemical exposure	Details of exposure	Cohort	Findings
	Postnatal (6 months – 5 years)	US (CHAMCOS; California)	– Attention problems and ADHD behaviours (CBCL) at 2 years (n=356)[145], 3.5 years (n=331)[146] and 5 years (n=323)[146] – Observed ADHD behaviours (Hillside) at 5 years (n=322)[146] – Sustained attention, response inhibition, alertness (CPT) at 5 years (n=312)[146] – Working memory (WISC) at 7 years (n=298)[147]
	Prenatal	US (CHAMCOS; California)	– Attention problems and ADHD behaviours (CBCL) at 2 years (n=356)[145] and 3.5 years (n=331)[146] ↑ Attention problems and ADHD behaviours (CBCL) at 5 years (n=323)[146] ↑ Observed ADHD behaviours (Hillside) at 5 years (n=322)[146] – Sustained attention, response inhibition, alertness (CPT) at 5 years (n=312)[146] ↓ Working memory (WISC) at 7 years (n=298)[147]
		US (Mount Sinai; NYC)	– Working memory (WISC) at 7-9 years (n=114)[139]
	Prenatal chlorpyrifos	US (CCCEH; NYC)	↑ Attention problems and ADHD behaviours (CBCL) at 3 years (n=228)[148] ↓ Working memory (WISC) at 7 years (n=265)[149]
		US (CHAMCOS; California)	– Attention problems and ADHD behaviours (CBCL) at 2 years (n=356)[145]
Polybrominated diphenyl ethers (PBDEs)	Prenatal PBDE 47, 99, 100, 153, 154	Netherlands (COMPARE)	↓ Sustained attention (TEA-Ch) at 5-6 years (n=60)[62] – Inhibition (NEPSY-II) at 5-6 years (n=60)[62] – Externalising behaviours (CBCL) and ADHD behaviours at 5-6 years (n=62)[62]
	Prenatal PBDE 47	Spain (Menorca)	– Inattention behaviours (DSM-IV) at 4 years (n=77)[150] – Executive function (McCarthy Scales) at 4 years (n=79)[150]
	Postnatal (breast milk) PBDE 28, 47, 99, 100, 153	US (PIN Babies Study; N Carolina)	↑ Externalising behaviours, specifically activity/impulsivity behaviours (ITSEA) at 30 months (n=222)[151]
	Current PBDE 47, 99,100, 153, 209	Belgium	– Sustained attention, response inhibition, alertness (NES-3 CPT) at 13-17 years (n=489)[55] – Working memory (NES-3) at 13-17 years (n=499)[55]
Manganese	Well water	Bangladesh (children of HEALS)	↑ Externalising behaviours (CBCL) at 8-11 years (n=201)[152]
	Current (blood)	Bangladesh (children of HEALS)	– Externalising behaviours (CBCL) at 8-11 years (n=201)[152]
	Current (hair)	Canada (Quebec)	↑ Oppositional & hyperactive behaviours (CRS-R) at 6-15 years (n=46)[153] – inattention behaviours (CRS-R) at 6-15 years (n=46)[153]
	Postnatal (7 months)	US (SECCYD)	↑ Externalising behaviours & attention problems (CBCL) at grade 1 & grade 3 (n=27)[154] – Total disruptive behaviours & ADHD behaviours (DSM-IV) at grade 3 (n=27)[154] – Response inhibition (forbidden toy task at 3 years; CPT at 4.5 years) (n=27)[154] – Cognitive flexibility (stroop) at 4.5 years (n=27)[154]
	Prenatal	US (SECCYD)	↑ Externalising behaviours & attention problems (CBCL) at grade 1 & at grade 3 (n=27)[154] ↑ Total disruptive behaviours & ADHD behaviours (DSM-IV) at grade 3 (n=27)[154] ↓ Response inhibition (forbidden toy task at 3 years; CPT at 4.5 years) (n=27)[154] ↓ Cognitive flexibility (stroop) at 4.5 years (n=27)[154]
Perfluorinated compounds	Current PFOA, PFOS, PFHxS, PFNA (12-15 years)	US (NHANES; 1999-2000, 2003-2004)	↑ ADHD diagnosis with PFOA, PFOS or PFHxS at 12-25 years (n=571)[155]
	Current PFOA, PFOS, PFHxS, PFNA	US (C8 Health Project)	↑ ADHD diagnosis with PFHxS at 5-18 years (n=10546) – ADHD diagnosis with PFOA, PFOS or PFNA at 5-18 years (n=10546)[156]

Table 1 continued.

Table 1. Chemicals where increased environmental exposure has been observed to be associated with increased externalising behaviours, with externalising disorders, or with information processing difficulties characteristic of ADHD (continued)

Chemical exposure	Details of exposure	Cohort	Findings
	Prenatal PFOA, PFOS	Denmark (DNBC)	– Externalising behaviours (SDQ; Hyperactivity & Conduct Problems) at 7 years (n=787)[157]
Nitrogen dioxide	Postnatal (3 months)	Spain (Menorca)	↑ Inattention behaviours (DSM-IV) at 4 years (n=398)[158] ↓ Executive function (McCarthy Scales) at 4 years (n=398)[158] – Sustained attention, response inhibition, alertness (CPT) at 11 years (n<393)[68]
	Current (school)	Netherlands (RANCH)	↓ Working memory (NES digit span) at 9-11 years (n=485)[159] – Working memory (NES SDST) & cognitive flexibility (NES SAT) at 9-11 years (n=485)[159]
	Current (home)	Netherlands (RANCH)	– Working memory & cognitive flexibility (NES) at 9-11 years (n=485)[159]
		UK (RANCH)	– Working memory (Search and Memory Task) at 9-10 years (n=580)[160]
Polycyclic aromatic hydrocarbons	Prenatal	US (CCCEH; NYC)	↑ Attention problems (CBCL) at 6-7 years (n=148-253)[161,162] Attention problems (CBCL) at 5 years (n=96)[162] – DSM-IV ADHD problems (CBCL) at 6-7 years (n=148-253)[161]
Hexachlorobenzene	Prenatal	Spain (Menorca)	↑ ADHD behaviours (DSM-IV) at 4 years (n=329)[163] – Sustained attention, response inhibition, alertness (CPT) at 11 years (n<393)[68]
		US (Oswego; NY)	– Response inhibition at 8 (CPT; n=174)[73] & 9.5 years (CPT & DRL; n=183)[73,104] – Working memory (WISC-III Freedom from Distractibility) at 9 years (n=155)[71]
	Postnatal (4 years)	Spain (Menora)	– Sustained attention, response inhibition, alertness (CPT) at 11 years (n<393)[68]
Trichlorophenols	2,4,6-TCP 2,4,5-TCP	US (NHANES; 1999-2004)	↑ ADHD diagnosis with 2,4,6-TCP but not 2,4,5-TCP at 6-15 years (n=2539)[164]

↓ denotes a statistically significant decrease in performance or score associated with increased chemical exposure ($p<0.05$); ↑ a statistically significant increase; – no statistically significant association. ADHD, Attention Deficit Hyperactivity Disorder; BASC, Behaviour Assessment System for Children; CPT, continuous performance test; DRL, Differential Reinforcement of Low Rates; CRS-R, Conners' Rating Scales-Revised; CBCL, Achenbach Child Behavior Checklist; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; WISC, Wechsler Intelligence Scale for Children; ITSEA, Infant-Toddler Social Emotional Assessment; SDQ, Strengths and Difficulties Questionnaire.

observational research, thus bridging the gap between observed association and biological causation. Looking forward, therefore, large-scale observational research, building on the experience of previous studies, continues to have a central role in generating and testing hypotheses in this important public health area.

References

1. Doshi JA, Hodgkins P, Kahle J, et al. Economic impact of childhood and adult attention-deficit/hyperactivity disorder in the United States. J Am Acad Child Adolesc Psychiatry 2012; 51(10):990-1002. e1002.
2. Boyle CA, Boulet S, Schieve LA, et al. Trends in the prevalence of developmental disabilities in US children, 1997-2008. Pediatrics 2011; 127(6):1034-42.
3. Hiscock H, Roberts G, Efron D, et al. Children Attending Paediatricians Study: a national prospective audit of outpatient practice from the Australian Paediatric Research Network. Med J Aust 2011; 194(8):392-7.
4. (APA) APA. Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR. Washington, DC: American Psychiatric Association; 2000.
5. Frick PJ, Lahey BB, Loeber R, et al. Oppositional defiant disorder and conduct disorder: A meta-analytic review of factor analyses and cross-validation in a clinic sample. Clin Psychol Rev 1993; 13(4):319-40.
6. (WHO) WHO. The ICD-10 classification of mental and behavioural disorders: diagnostic criteria for research: World Health Organization; 1993.
7. Scassellati C, Bonvicini C, Faraone SV, et al. Biomarkers and attention-deficit/hyperactivity disorder: a systematic review and meta-analyses. J Am Acad Child Adolesc Psychiatry 2012; 51(10):1003-19. e1020.
8. Levy F, Hay DA, McStephen M, et al. Attention-deficit hyperactivity disorder: a category or a continuum? Genetic analysis of a large-scale twin study. J Am Acad Child Adolesc Psychiatry 1997; 36(6):737-44.
9. Nigg JT, Blaskey LG, Stawicki JA, et al. Evaluating the endophenotype model of ADHD neuropsychological deficit: results for parents and siblings of children with ADHD combined and inattentive subtypes. J Abnorm Psychol 2004; 113(4):614-25.
10. Aguiar A, Eubig PA, Schantz SL. Attention deficit/hyperactivity disorder: a focused overview for children's environmental health researchers. Environ Health Perspect 2010; 118(12):1646-53.
11. Achenbach T, Rescorla L. Child behavior checklist for ages 6-18. Burlington, VT: Achenbach System of Empirically Based Assessment (ASEBA); 2001.
12. Goodman R. Psychometric properties of the strengths and difficulties questionnaire. J Am Acad Child Adolesc Psychiatry 2001; 40(11):1337-45.
13. Conners C. Conners' rating scales-revised: technical manual. New York: Multi-Health Systems Incorporated; 1997.
14. Carter AS, Briggs-Gowan MJ, Jones SM, et al. The Infant-Toddler Social and Emotional Assessment (ITSEA): factor structure, reliability, and validity. J Abnorm Child Psychol 2003; 31(5):495-514.
15. Reynolds C, Kamphaus R. Behavior assessment system for children 2nd ed. Bloomington, MN: Pearson Assessments; 2004.
16. Barkley RA. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull 1997; 121(1):65-94.
17. Nigg JT. Attention-deficit/hyperactivity disorder endophenotypes, structure, and etiological pathways. Curr Dir Psychol Sci 2010; 19(1):24-9.
18. Pennington BF, Ozonoff S. Executive functions and developmental psychopathology. J Child Psychol Psychiatry 1996; 37(1):51-87.
19. Mahone EM, Schneider HE. Assessment of attention in preschoolers. Neuropsychol Rev 2012; 22(4):361-83.
20. Anderson PJ, Reidy N. Assessing executive function in preschoolers. Neuropsychol Rev 2012; 22(4):345-60.
21. Eubig PA, Aguiar A, Schantz SL. Lead and PCBs as risk factors for attention deficit/hyperactivity disorder. Environ Health Perspect 2010; 118(12):1654-67.
22. Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. Lancet 2006; 368(9553):2167-78.
23. Banerjee TD, Middleton F, Faraone SV. Environmental risk factors for attention-deficit hyperactivity disorder. Acta Paediatr 2007; 96(9):1269-74.

24. Williams JHG, Ross L. Consequences of prenatal toxin exposure for mental health in children and adolescents. Eur Child Adolesc Psychiatry 2007; 16(4):243-53.
25. Miodovnik A, Engel SM, Zhu C, et al. Endocrine disruptors and childhood social impairment. Neurotoxicology 2011; 32(2):261-7.
26. Needleman HL, Gunnoe C, Leviton A, et al. Deficits in psychologic and classroom performance of children with elevated dentine lead levels. N Engl J Med 1979; 300(13):689-95.
27. Canfield RL, Henderson CR, Jr., Cory-Slechta DA, et al. Intellectual impairment in children with blood lead concentrations below 10 microg per deciliter. N Engl J Med 2003; 348(16):1517-26.
28. Lanphear BP, Hornung R, Khoury J, et al. Low-Level Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis. Environ Health Perspect 2005; 113(7):894-9.
29. Jusko TA, Henderson CR, Lanphear BP, et al. Blood lead concentrations < 10 microg/dL and child intelligence at 6 years of age. Environ Health Perspect 2008;116(2):243-248.
30. Schnaas L, Rothenberg SJ, Flores MF, et al. Reduced intellectual development in children with prenatal lead exposure. Environ Health Perspect 2006; 114(5):791-7.
31. Wasserman GA, Liu X, Popovac D, et al. The Yugoslavia Prospective Lead Study: contributions of prenatal and postnatal lead exposure to early intelligence. Neurotoxicol Teratol 2000; 22(6):811-8.
32. Wasserman GA, Liu X, Lolacono NJ, et al. Lead exposure and intelligence in 7-year-old children: the Yugoslavia Prospective Study. Environ Health Perspect 1997; 105(9):956-62.
33. Tong S, Baghurst P, McMichael A, et al. Lifetime exposure to environmental lead and children's intelligence at 11-13 years: the Port Pirie cohort study. BMJ 1996; 312(7046):1569-75.
34. Tong S, Baghurst PA, Sawyer MG, et al. Declining blood lead levels and changes in cognitive function during childhood: the Port Pirie Cohort Study. JAMA 1998; 280(22):1915-9.
35. Huang PC, Su PH, Chen HY, et al. Childhood blood lead levels and intellectual development after ban of leaded gasoline in Taiwan: a 9-year prospective study. Environ Int 2012; 40:88-96.
36. Baghurst PA, McMichael AJ, Wigg NR, et al. Environmental exposure to lead and children's intelligence at the age of seven years. The Port Pirie Cohort Study. N Engl J Med 1992; 327(18):1279-84.
37. Chiodo LM, Covington C, Sokol RJ, et al. Blood lead levels and specific attention effects in young children. Neurotoxicol Teratol 2007; 29(5):538-46.
38. Chiodo LM, Jacobson SW, Jacobson JL. Neurodevelopmental effects of postnatal lead exposure at very low levels. Neurotoxicol Teratol 2004; 26(3):359-71.
39. Needleman HL, Riess JA, Tobin MJ, et al. Bone lead levels and delinquent behavior. JAMA 1996; 275(5):363-9.
40. Tuthill RW. Hair lead levels related to children's classroom attention-deficit behavior. Arch Environ Health 1996; 51(3):214-20.
41. Naicker N, Richter L, Mathee A, et al. Environmental lead exposure and socio-behavioural adjustment in the early teens: the birth to twenty cohort. Sci Total Environ 2012; 414:120-5.
42. Sciarillo WG, Alexander G, Farrell KP. Lead exposure and child behavior. Am J Public Health 1992; 82(10):1356-60.
43. Mendelsohn AL, Dreyer BP, Fierman AH, et al. Low-level lead exposure and behavior in early childhood. Pediatrics 1998; 101(3):E10.
44. Braun JM, Froehlich TE, Daniels JL, et al. Association of environmental toxicants and conduct disorder in U.S. children: NHANES 2001-2004. Environ Health Perspect 2008; 116(7):956-62.
45. Froehlich TE, Lanphear BP, Auinger P, et al. Association of tobacco and lead exposures with attention-deficit/hyperactivity disorder. Pediatrics 2009; 124(6):e1054-63.
46. Braun JM, Kahn RS, Froehlich T, et al. Exposures to environmental toxicants and attention deficit hyperactivity disorder in US children. Environ Health Perspect 2006; 114(12):1904.
47. Dietrich KN, Ris MD, Succop PA, et al. Early exposure to lead and juvenile delinquency. Neurotoxicol Teratol 2001; 23(6):511-8.
48. Wasserman GA, Staghezza-Jaramillo B, Shrout P, et al. The effect of lead exposure on behavior problems in preschool children. Am J Public Health 1998; 88(3):481-6.
49. Bellinger D, Leviton A, Allred E, et al. Pre- and postnatal lead exposure and behavior problems in school-aged children. Environ Res 1994; 66(1):12-30.
50. Chen A, Cai B, Dietrich KN, et al. Lead exposure, IQ, and behavior in urban 5- to 7-year-olds: does lead affect behavior only by lowering IQ? Pediatrics 2007; 119(3):e650-8.
51. Plusquellec P, Muckle G, Dewailly E, et al. The relation of environmental contaminants exposure to behavioral indicators in Inuit preschoolers in Arctic Quebec. Neurotoxicology 2010; 31(1):17-25.
52. Boucher O, Jacobson SW, Plusquellec P, et al. Prenatal methylmercury, postnatal lead exposure, and evidence of attention deficit/hyperactivity disorder among Inuit children in Arctic Quebec. Environ Health Perspect 2012; 120(10):1456-61.
53. Nigg JT, Knottnerus GM, Martel MM, et al. Low blood lead levels associated with clinically diagnosed attention-deficit/hyperactivity disorder and mediated by weak cognitive control. Biol Psychiatry 2008; 63(3):325-31.
54. Boucher O, Burden MJ, Muckle G, et al. Response inhibition and error monitoring during a visual go/no-go task in inuit children exposed to lead, polychlorinated biphenyls, and methylmercury. Environ Health Perspect 2012; 120(4):608-15.
55. Kicinski M, Viaene MK, Den Hond E, et al. Neurobehavioral function and low-level exposure to brominated flame retardants in adolescents: a cross-sectional study. Environ Health 2012; 11:86.
56. Hansen ON, Trillingsgaard A, Beese I, et al. A neuropsychological study of children with elevated dentine lead level: assessment of the effect of lead in different socio-economic groups. Neurotoxicol Teratol 1989; 11(3):205-13.
57. (ATSDR) AfTSaDR. Toxicological profile for polychlorinated biphenyls (PCBs). Atlanta, GA: US Department of Health and Human Services, Public Health Service; 2000.
58. UNEP. The stockholm convention on persistent organic pollutants. Paper presented at: Stockholm convention on persistent oganic pollutants, 2001; Stockholm.
59. Yu ML, Hsu CC, Guo YL, et al. Disordered behavior in the early-born Taiwan Yucheng children. Chemosphere 1994; 29(9-11):2413-22.
60. Lai TJ, Liu X, Guo YL, et al. A cohort study of behavioral problems and intelligence in children with high prenatal polychlorinated biphenyl exposure. Arch Gen Psychiatry 2002; 59(11):1061-6.
61. Sagiv SK, Thurston SW, Bellinger DC, et al. Prenatal organochlorine exposure and behaviors associated with attention deficit hyperactivity disorder in school-aged children. Am J Epidemiol 2010; 171(5):593-601.
62. Roze E, Meijer L, Bakker A, et al. Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioral performance at school age. Environ Health Perspect 2009; 117(12):1953-8.
63. Jusko T, Sovcikova E, Drobna B, et al. Pre-and postnatal PCB concentrations and child behavior at age 45 months. Epidemiology 2009; 20(6):S92.
64. Boucher O, Muckle G, Bastien CH. Prenatal exposure to polychlorinated biphenyls: a neuropsychologic analysis. Environ Health Perspect 2009; 117(1):7-16.
65. Grandjean P, Weihe P, Burse VW, et al. Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. Neurotoxicol Teratol 2001; 23(4):305-17.
66. Debes F, Budtz-Jorgensen E, Weihe P, et al. Impact of prenatal methylmercury exposure on neurobehavioral function at age 14 years. Neurotoxicol Teratol 2006; 28(3):363-75.
67. Sagiv SK, Thurston SW, Bellinger DC, et al. Neuropsychological measures of attention and impulse control among 8-year-old children exposed prenatally to organochlorines. Environ Health Perspect 2012; 120(6):904-9.
68. Forns J, Torrent M, Garcia-Esteban R, et al. Longitudinal association between early life socio-environmental factors and attention function at the age 11 years. Environ Res 2012; 117:54-59.
69. Jacobson JL, Jacobson SW. Prenatal exposure to polychlorinated biphenyls and attention at school age. J Pediatr 2003; 143(6):780-8.
70. Vreugdenhil HJ, Lanting CI, Mulder PG, et al. Effects of prenatal PCB and dioxin background exposure on cognitive and motor abilities in Dutch children at school age. J Pediatr 2002; 140(1):48-56.
71. Stewart PW, Lonky E, Reihman J, et al. The relationship between prenatal PCB exposure and intelligence (IQ) in 9-year-old children. Environ Health Perspect 2008; 116(10):1416-22.
72. Stewart P, Fitzgerald S, Reihman J, et al. Prenatal PCB exposure, the corpus callosum, and response inhibition. Environmental Health Perspectives 2003; 111(13):1670-7.
73. Stewart P, Reihman J, Gump B, et al. Response inhibition at 8 and 9 1/2 years of age in children prenatally exposed to PCBs. Neurotoxicol Teratol 2005; 27(6):771-80.
74. Rice DC. Behavioral impairment produced by low-level postnatal PCB exposure in monkeys. Environ Res 1999; 80(2 Pt 2):S113-21.
75. Jacobson JL, Jacobson SW, Humphrey HE. Effects of exposure to PCBs and related compounds on growth and activity in children. Neurotoxicol Teratol 1990; 12(4):319-26.
76. Patandin S, Lanting CI, Mulder PG, et al. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. J Pediatr 1999; 134(1):33-41.
77. Walkowiak J, Wiener JA, Fastabend A, et al. Environmental exposure to polychlorinated biphenyls and quality of the home environment: effects on psychodevelopment in early childhood. The Lancet 2001; 358(9293):1602-7.
78. Vreugdenhil HJ, Mulder PG, Emmen HH, et al. Effects of perinatal exposure to PCBs on neuropsychological functions in the Rotterdam cohort at 9 years of age. Neuropsychology 2004; 18(1):185-93.
79. Jacobson JL, Jacobson SW. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N Engl J Med 1996; 335(11):783-9.
80. Lee DH, Jacobs DR, Porta M. Association of serum concentrations of persistent organic pollutants with the prevalence of learning disability and attention deficit disorder. J Epidemiol Community Health 2007; 61(7):591-6.
81. Schantz SL, Widholm JJ, Rice DC. Effects of PCB exposure on neuropsychological function in children. Environ Health Perspect 2003; 111(3):357-76.
82. Park HY, Hertz-Picciotto I, Sovcikova E, et al. Neurodevelopmental toxicity of prenatal polychlorinated biphenyls (PCBs) by chemical structure and activity: a birth cohort study. Environ Health 2010; 9:51.
83. Newman J, Gallo MV, Schell LM, et al. Analysis of PCB congeners related to cognitive functioning in adolescents. Neurotoxicology 2009; 30(4):686-96.
84. UNEP. Global mercury assessment report. Geneva, Switzerland: United Nations Environment Programme Chemicals; 2002.
85. Grandjean P, Satoh H, Murata K, et al. Adverse effects of methylmercury: environmental health research implications. Environ Health Perspect 2010;

118(8):1137-45.
86. Davidson PW, Cory-Slechta DA, Thurston SW, et al. Fish consumption and prenatal methylmercury exposure: cognitive and behavioral outcomes in the main cohort at 17 years from the Seychelles child development study. Neurotoxicology 2011; 32(6):711-7.
87. Crump KS, Kjellstrom T, Shipp AM, et al. Influence of prenatal mercury exposure upon scholastic and psychological test performance: benchmark analysis of a New Zealand cohort. Risk Anal 1998; 18(6):701-13.
88. Sagiv SK, Thurston SW, Bellinger DC, et al. Prenatal exposure to mercury and fish consumption during pregnancy and attention-deficit/hyperactivity disorder-related behavior in children. Arch Pediatr Adolesc Med 2012; 166(12):1123-31.
89. Lederman SA, Jones RL, Caldwell KL, et al. Relation between cord blood mercury levels and early child development in a World Trade Center cohort. Environ Health Perspect 2008; 116(8):1085-91.
90. Oken E, Radesky JS, Wright RO, et al. Maternal fish intake during pregnancy, blood mercury levels, and child cognition at age 3 years in a US cohort. Am J Epidemiol 2008; 167(10):1171-81.
91. Jedrychowski W, Jankowski J, Flak E, et al. Effects of prenatal exposure to mercury on cognitive and psychomotor function in one-year-old infants: epidemiologic cohort study in Poland. Ann Epidemiol 2006; 16(6):439-47.
92. Llop S, Guxens M, Murcia M, et al. Prenatal exposure to mercury and infant neurodevelopment in a multicenter cohort in Spain: study of potential modifiers. Am J Epidemiol 2012; 175(5):451-65.
93. Davidson PW, Strain JJ, Myers GJ, et al. Neurodevelopmental effects of maternal nutritional status and exposure to methylmercury from eating fish during pregnancy. Neurotoxicology 2008;29(5):767-775.
94. Freire C, Ramos R, Lopez-Espinosa MJ, et al. Hair mercury levels, fish consumption, and cognitive development in preschool children from Granada, Spain. Environ Res 2010; 110(1):96-104.
95. Lynch ML, Huang LS, Cox C, et al. Varying coefficient function models to explore interactions between maternal nutritional status and prenatal methylmercury toxicity in the Seychelles Child Development Nutrition Study. Environ Res 2011; 111(1):75-80.
96. Davidson PW, Myers GJ, Cox C, et al. Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment: outcomes at 66 months of age in the Seychelles Child Development Study. JAMA 1998; 280(8):701-7.
97. Myers GJ, Davidson PW, Palumbo D, et al. Secondary analysis from the Seychelles Child Development Study: the child behavior checklist. Environ Res 2000; 84(1):12-9.
98. Myers GJ, Davidson PW, Cox C, et al. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. The Lancet 2003; 361(9370):1686-92.
99. Cao Y, Chen A, Jones RL, et al. Does background postnatal methyl mercury exposure in toddlers affect cognition and behavior? Neurotoxicology 2010; 31(1):1-9.
100. Diamond A, Doar B. The performance of human infants on a measure of frontal cortex function, the delayed response task. Dev Psychobiol 1989; 22(3):271-94.
101. Palumbo DR, Cox C, Davidson PW, et al. Association between prenatal exposure to methylmercury and cognitive functioning in Seychellois children: a reanalysis of the McCarthy Scales of Children's Ability from the main cohort study. Environ Res 2000; 84(2):81-8.
102. Grandjean P, Budtz-Jorgensen E, White RF, et al. Methylmercury exposure biomarkers as indicators of neurotoxicity in children aged 7 years. Am J Epidemiol 1999; 150(3):301-5.
103. Grandjean P, Weihe P, White RF, et al. Cognitive performance of children prenatally exposed to "safe" levels of methylmercury. Environ Res 1998; 77(2):165-72.
104. Stewart PW, Sargent DM, Reihman J, et al. Response inhibition during Differential Reinforcement of Low Rates (DRL) schedules may be sensitive to low-level polychlorinated biphenyl, methylmercury, and lead exposure in children. Environ Health Perspect 2006; 114(12):1923-9.
105. Stewart PW, Reihman J, Lonky EI, et al. Cognitive development in preschool children prenatally exposed to PCBs and MeHg. Neurotoxicol Teratol 2003; 25(1):11-22.
106. Julvez J, Ribas-Fito N, Torrent M, et al. Maternal smoking habits and cognitive development of children at age 4 years in a population-based birth cohort. Int J Epidemiol 2007; 36(4):825-32.
107. Langley K, Rice F, van den Bree MB, et al. Maternal smoking during pregnancy as an environmental risk factor for attention deficit hyperactivity disorder behaviour. A review. Minerva Pediatr 2005; 57(6):359-71.
108. Tiesler CM, Chen CM, Sausenthaler S, et al. Passive smoking and behavioural problems in children: results from the LISAplus prospective birth cohort study. Environ Res 2011; 111(8):1173-9.
109. Jedrychowski W, Maugeri U, Perera F, et al. Cognitive function of 6-year old children exposed to mold-contaminated homes in early postnatal period. Prospective birth cohort study in Poland. Physiol Behav 2011; 104(5):989-95.
110. Hsieh CJ, Jeng SF, Su YN, et al. CYP1A1 modifies the effect of maternal exposure to environmental tobacco smoke on child behavior. Nicotine Tob Res 2010; 12(11):1108-17.
111. Ruckinger S, Rzehak P, Chen CM, et al. Prenatal and postnatal tobacco exposure and behavioral problems in 10-year-old children: results from the GINI-plus prospective birth cohort study. Environ Health Perspect 2010; 118(1):150-4.
112. Brion MJ, Victora C, Matijasevich A, et al. Maternal smoking and child psychological problems: disentangling causal and noncausal effects. Pediatrics 2010; 126(1):e57-65.
113. Langley K, Heron J, Smith GD, et al. Maternal and paternal smoking during pregnancy and risk of ADHD symptoms in offspring: testing for intrauterine effects. Am J Epidemiol 2012; 176(3):261-8.
114. Thapar A, Rice F, Hay D, et al. Prenatal smoking might not cause attention-deficit/hyperactivity disorder: evidence from a novel design. Biol Psychiatry 2009; 66(8):722-7.
115. Maughan B, Taylor A, Caspi A, et al. Prenatal smoking and early childhood conduct problems: testing genetic and environmental explanations of the association. Arch Gen Psychiatry 2004; 61(8):836-43.
116. Buschgens CJ, Swinkels SH, van Aken MA, et al. Externalizing behaviors in preadolescents: familial risk to externalizing behaviors, prenatal and perinatal risks, and their interactions. Eur Child Adolesc Psychiatry 2009; 18(2):65-74.
117. Hsieh CJ, Liao HF, Wu KY, et al. CYP1A1 Ile462Val and GSTT1 modify the effect of cord blood cotinine on neurodevelopment at 2 years of age. Neurotoxicology 2008; 29(5):839-45.
118. Jones RL, Homa DM, Meyer PA, et al. Trends in blood lead levels and blood lead testing among US children aged 1 to 5 years, 1988-2004. Pediatrics 2009; 123(3):e376-85.
119. Noren K, Meironyte D. Certain organochlorine and organobromine contaminants in Swedish human milk in perspective of past 20-30 years. Chemosphere 2000; 40(9-11):1111-23.
120. Zietz BP, Hoopmann M, Funcke M, et al. Long-term biomonitoring of polychlorinated biphenyls and organochlorine pesticides in human milk from mothers living in northern Germany. Int J Hyg Environ Health 2008; 211(5-6):624-38.
121. (CDC) CfDCaP. Trends in Current Cigarette Smoking Among High School Students and Adults, United States, 1965–2011. Atlanta, GA 7th December 2012 2012.
122. (EPA) USEPA. What are the trends in exposure to environmental contaminants including across population subgroups and geographic regions? Report on the Environment [June 2010; http://cfpub.epa.gov/eroe/index.cfm?fuseaction=detail.viewInd&lv=list.listbyalpha&r=224031&subtop=208. Accessed 05/03/2013, 2013.
123. Meeker JD. Exposure to environmental endocrine disruptors and child development. Arch Pediatr Adolesc Med 2012; 166(6):E1-7.
124. Vandenberg LN, Colborn T, Hayes TB, et al. Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses. Endocr Rev 2012; 33(3):378-455.
125. Kang JH, Kondo F, Katayama Y. Human exposure to bisphenol A. Toxicology 2006; 226(2-3):79-89.
126. Kubwabo C, Kosarac I, Stewart B, et al. Migration of bisphenol A from plastic baby bottles, baby bottle liners and reusable polycarbonate drinking bottles. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2009; 26(6):928-37.
127. Geens T, Goeyens L, Covaci A. Are potential sources for human exposure to bisphenol-A overlooked? Int J Hyg Environ Health 2011; 214(5):339-47.
128. Braun JM, Kalkbrenner AE, Calafat AM, et al. Impact of early-life bisphenol A exposure on behavior and executive function in children. Pediatrics 2011; 128(5):873-82.
129. Perera F, Vishnevetsky J, Herbstman JB, et al. Prenatal bisphenol a exposure and child behavior in an inner-city cohort. Environ Health Perspect 2012; 120(8):1190-4.
130. Braun JM, Yolton K, Dietrich KN, et al. Prenatal bisphenol A exposure and early childhood behavior. Environ Health Perspect 2009; 117(12):1945-52.
131. Ha M, Ha EH, Lee BE, et al. Prenatal Exposure to polycyclic aromatic hydrocarbons, bisphenol A, and phthalates and growth and neurodevelopment in infants and children. Epidemiology 2011; 22(1):S57.
132. NICNAS. Phthalates: National Industrial Chemicals Notification and Assessment Scheme, Australian Government Department of Health and Ageing; 2009.
133. Kim BN, Cho SC, Kim Y, et al. Phthalates exposure and attention-deficit/hyperactivity disorder in school-age children. Biol Psychiatry 2009; 66(10):958-63.
134. Whyatt RM, Liu X, Rauh VA, et al. Maternal prenatal urinary phthalate metabolite concentrations and child mental, psychomotor, and behavioral development at 3 years of age. Environ Health Perspect 2012; 120(2):290-5.
135. Engel SM, Miodovnik A, Canfield RL, et al. Prenatal phthalate exposure is associated with childhood behavior and executive functioning. Environ Health Perspect 2010; 118(4):565-71.
136. Yolton K, Xu Y, Strauss D, et al. Prenatal exposure to bisphenol A and phthalates and infant neurobehavior. Neurotoxicol Teratol 2011; 33(5):558-66.
137. Kim Y, Ha EH, Kim EJ, et al. Prenatal exposure to phthalates and infant development at 6 months: prospective Mothers and Children's Environmental Health (MOCEH) study. Environ Health Perspect 2011; 119(10):1495-500.
138. Eskenazi B, Huen K, Marks A, et al. PON1 and neurodevelopment in children from the CHAMACOS study exposed to organophosphate pesticides in utero. Environ Health Perspect 2010; 118(12):1775-81.
139. Engel SM, Wetmur J, Chen J, et al. Prenatal exposure to organophosphates, paraoxonase 1, and cognitive development in childhood. Environ Health Perspect 2011; 119(8):1182-8.
140. Morales E, Sunyer J, Castro-Giner F, et al. Influence of glutathione S-transferase polymorphisms on cognitive functioning effects induced by p,p'-DDT among preschoolers. Environ Health Perspect 2008; 116(11):1581-5.
141. Wise A, Parham F, Axelrad DA, et al. Upstream adverse effects in risk assessment: a model of polychlorinated biphenyls, thyroid hormone disruption and neurological outcomes in humans. Environ Res 2012; 117:90-9.

142. Bouchard MF, Bellinger DC, Wright RO, et al. Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. Pediatrics 2010; 125(6):e1270-7.
143. Harari R, Julvez J, Murata K, et al. Neurobehavioral deficits and increased blood pressure in school-age children prenatally exposed to pesticides. Environ Health Perspect 2010; 118(6):890-6.
144. Abdel Rasoul GM, Abou Salem ME, Mechael AA, et al. Effects of occupational pesticide exposure on children applying pesticides. Neurotoxicology 2008; 29(5):833-8.
145. Eskenazi B, Marks AR, Bradman A, et al. Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children. Environ Health Perspect 2007; 115(5):792-8.
146. Marks AR, Harley K, Bradman A, et al. Organophosphate pesticide exposure and attention in young Mexican-American children: the CHAMACOS study. Environ Health Perspect 2010; 118(12):1768-74.
147. Bouchard MF, Chevrier J, Harley KG, et al. Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. Environ Health Perspect 2011; 119(8):1189-95.
148. Rauh VA, Garfinkel R, Perera FP, et al. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. Pediatrics 2006; 118(6):e1845-59.
149. Rauh V, Arunajadai S, Horton M, et al. Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. Environ Health Perspect 2011; 119(8):1196-201.
150. Gascon M, Vrijheid M, Martinez D, et al. Effects of pre and postnatal exposure to low levels of polybromodiphenyl ethers on neurodevelopment and thyroid hormone levels at 4 years of age. Environ Int 2011; 37(3):605-11.
151. Hoffman K, Adgent M, Goldman BD, et al. Lactational exposure to polybrominated diphenyl ethers and its relation to social and emotional development among toddlers. Environ Health Perspect 2012; 120(10):1438-42.
152. Khan K, Factor-Litvak P, Wasserman GA, et al. Manganese exposure from drinking water and children's classroom behavior in Bangladesh. Environ Health Perspect 2011; 119(10):1501-6.
153. Bouchard M, Laforest F, Vandelac L, et al. Hair manganese and hyperactive behaviors: pilot study of school-age children exposed through tap water. Environmental Health Perspectives 2007; 115(1):122.
154. Ericson JE, Crinella FM, Clarke-Stewart KA, et al. Prenatal manganese levels linked to childhood behavioral disinhibition. Neurotoxicol Teratol 2007; 29(2):181-7.
155. Hoffman K, Webster TF, Weisskopf MG, et al. Exposure to polyfluoroalkyl chemicals and attention deficit/hyperactivity disorder in U.S. children 12-15 years of age. Environ Health Perspect 2010; 118(12):1762-7.
156. Stein CR, Savitz DA. Serum perfluorinated compound concentration and attention deficit/hyperactivity disorder in children 5-18 years of age. Environmental Health Perspectives 2011; 119(10):1466.
157. Fei C, Olsen J. Prenatal exposure to perfluorinated chemicals and behavioral or coordination problems at age 7 years. Environ Health Perspect 2011; 119(4):573-8.
158. Morales E, Julvez J, Torrent M, et al. Association of early-life exposure to household gas appliances and indoor nitrogen dioxide with cognition and attention behavior in preschoolers. Am J Epidemiol 2009; 169(11):1327-36.
159. van Kempen E, Fischer P, Janssen N, et al. Neurobehavioral effects of exposure to traffic-related air pollution and transportation noise in primary schoolchildren. Environ Res 2012; 115:18-25.
160. Clark C, Crombie R, Head J, et al. Does traffic-related air pollution explain associations of aircraft and road traffic noise exposure on children's health and cognition? A secondary analysis of the United Kingdom sample from the RANCH project. Am J Epidemiol 2012; 176(4):327-37.
161. Perera FP, Tang D, Wang S, et al. Prenatal polycyclic aromatic hydrocarbon (PAH) exposure and child behavior at age 6-7 years. Environ Health Perspect 2012; 120(6):921-6.
162. Perera FP, Wang S, Vishnevetsky J, et al. Polycyclic aromatic hydrocarbons-aromatic DNA adducts in cord blood and behavior scores in New York city children. Environ Health Perspect 2011; 119(8):1176-81.
163. Ribas-Fito N, Torrent M, Carrizo D, et al. Exposure to hexachlorobenzene during pregnancy and children's social behavior at 4 years of age. Environ Health Perspect 2007; 115(3):447-50.
164. Xu X, Nembhard WN, Kan H, et al. Urinary trichlorophenol levels and increased risk of attention deficit hyperactivity disorder among US school-aged children. Occup Environ Med 2011; 68(8):557-61.