NeuroToxicology 54 (2016) 89–98

Contents lists available at ScienceDirect

NeuroToxicology

Full length article

Bisphenol A, phthalates and lead and learning and behavioral problems in Canadian children 6–11 years of age: CHMS 2007–2009

Tye E. Arbuckle[a,*], Karelyn Davis[a], Khrista Boylan[b], Mandy Fisher[a], Jingshan Fu[a]

[a] Population Studies Division, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, ON, Canada
[b] Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada

ARTICLE INFO

Article history:
Received 8 July 2015
Received in revised form 21 March 2016
Accepted 22 March 2016
Available online 25 March 2016

Keywords:
Lead
Bisphenol A
Phthalates
Children
Behavior
Learning difficulties

ABSTRACT

Childhood developmental disorders and related problems such as learning disabilities and attention deficit hyperactivity disorder (ADHD) account for a growing burden on the family, education and health care systems. Exposure to environmental chemicals such as bisphenol A (BPA) and phthalates may play a role in the development of child behavioral problems. Using cross-sectional data from Cycle 1 of the Canadian Health Measures Survey (CHMS), we examined the potential association between urinary concentrations of BPA and various phthalate metabolites and child learning and behavioral problems, considering important covariates such as gender, blood lead and environmental tobacco smoke (ETS). The Strengths and Difficulties Questionnaire (SDQ) outcomes of interest were emotional symptoms, hyperactivity/inattention, and a total difficulties score with borderline and abnormal scores grouped together and compared with children with normal scores. Other outcomes studied included any reported learning disability, a subset of learning disabilities reported as ADD/ADHD (attention deficit disorder) and use of psychotropic medications in the past month.

Among children ages 6–11 years, the prevalences of any learning disability, ADD, and ADHD were 8.7%, 1.5% and 2.8%, respectively. Estimated prevalences for SDQ hyperactivity/inattention, emotional symptoms and total difficulties scores were 16.9%, 15.0%, and 13.0%, respectively.

Child's urinary BPA was associated with taking psychotropic medications (OR 1.59; 95% CI 1.05–2.40). Urinary MBzP concentration was significantly associated with emotional symptoms in girls (OR 1.38 95% CI 1.09–1.75) but not in boys (OR 1.05 95% CI 0.82–1.36).) Blood lead was significantly associated with several of the outcomes examined, with a significant interaction observed between prenatal smoking and blood lead for the total difficulties score (OR = 10.57; 95% CI 2.81–39.69 vs. OR = 1.98; 95% CI 1.41–2.79 if mother did not smoke during pregnancy).

Although limited by the cross-sectional nature of the study which precludes examining causation, the results suggest that although some indicators of child behavior were significantly associated with their urinary BPA and phthalate concentrations, the major chemical associated with adverse behavioral indicators was lead.

1. Introduction

Childhood developmental disorders and related problems such as learning disabilities and attention deficit hyperactivity disorder (ADHD) account for a growing burden on the family, and the education and health care systems. Children with these problems may be at increased risk for antisocial behavior, lower educational attainment, criminality and drug abuse later in life (Kessler et al., 1995; Copeland et al., 2013, 2007; Levy et al., 2014; Dalsgaard et al., 2013).

In 2006, a disability related to learning affected 3.2% of all children aged 5–14 in Canada (Statistics Canada, 2008). Approximately 1 in 6 children in the United States (2006–2008) reportedly had a developmental disability ranging from mild to serious (Boyle et al., 2011), highlighting the significant public health and economic impact on society and the family. The prevalence of learning disabilities, ADHD and other development delays in the US was 7.66%, 6.69% and 3.65%, respectively, with significant increases in rates over the past 12 years (Boyle et al., 2011).

The etiology of developmental disorders such as ADHD is multifactorial, which underlies the importance of studying both

* Corresponding author.
E-mail address: tye.arbuckle@hc-sc.gc.ca (T.E. Arbuckle).

http://dx.doi.org/10.1016/j.neuro.2016.03.014

genetic and environmental factors and their interactions (Becker et al., 2008). The potential role of exposure to environmental chemicals on the risk of developing child behavioral problems has been investigated in numerous studies of pre-, post-natal and concurrent exposures. As the brains of young children are inimitably sensitive to environmental chemicals at levels significantly lower than those harmful to adults (Winneke, 2011), it is critical to examine risks associated with ubiquitous emerging chemicals. A recent expert panel has concluded that exposures in Europe to endocrine disrupting chemicals contribute substantially to neurobehavioral deficits and disease, with estimated costs of > €150 billion/year (Bellanger et al., 2015).

Lead is the most frequently studied environmental chemical, with a recent meta-analysis supporting the association between lead exposure and hyperactivity/impulsivity symptoms (Goodlad et al., 2013). Prenatal exposure to tobacco smoke has also been associated with a number of adverse outcomes most significantly and consistently being increased risk of behavioral disorders such as ADHD (Abbott and Winzer-Serhan, 2012). As McCrory and Layte (2012) have argued, prenatal tobacco smoke exposure may increase risk for childhood behavioral problems through a number of pathways, such as direct effects on brain biochemistry or indirectly by increasing susceptibility to other risks; however, it is also possible that the findings result from failure to adequately account for important confounders (McCrory and Layte, 2012; Roza et al., 2009; Lavigne et al., 2011).

Recently, there is concern that exposure to chemicals (such as phthalates and bisphenol A (BPA)) in consumer products may be associated with risks for developmental disabilities. There are a number of different phthalates found in consumer products ranging from fragrances to adhesives, polyvinyl chloride (PVC) flooring and food packaging. For example, diethyl phthalate is a low molecular weight phthalate commonly used in cosmetics, while di-(2-ethylhexyl) phthalate has a high molecular weight and is commonly used as a plasticizer in PVC. BPA has been widely used in polycarbonate consumer products, including reusable water bottles and is also found in epoxy resins, which act as a protective lining on the inside of metal-based food and beverage cans (Government of Canada, http://www.chemicalsubstanceschimiques.gc.ca/challenge-defi/batch-lot-2/bisphenol-a/index-eng.php, accessed 05.01.15).

Several studies have previously examined the potential association between phthalates and BPA and developmental disabilities in children. A strong positive association has been observed between child urinary concentrations of metabolites of di-(2-ethylhexyl) phthalate (DEHP) and di-n-butyl phthalate (DnBP) and symptoms of ADHD (Kim et al., 2009). Urinary BPA has been positively associated with total problems score and negatively with learning quotient in school-age children (Hong et al., 2013). Both phthalates and BPA are considered endocrine modulating chemicals: phthalates are considered to function as anti-androgens, while BPA may act as an estrogen (Weiss, 2012).

The evidence to date suggests that early life exposure to environmental chemicals may be contributing factors in the development of child learning and behavioral disabilities. The major goal of this study was to explore the possible relationships between concurrent exposure to BPA or phthalates and several indicators of behavioral or learning difficulties in children. A secondary question was to consider whether any exposure risk remains significant or interacts with lead or passive tobacco exposure in a large population of children, which has rarely been done previously, thus addressing an important knowledge gap.

2. Methodology

2.1. Study population and data collected

The Canadian Health Measures Survey (CHMS) was designed to collect key information on the health of Canadians using direct physical measurements, collection of blood and urine and household and clinic interviews (Health Canada, 2010; Statistics Canada, 2011). The target population for Cycle 1 were individuals between 6 and 79 years of age living in privately occupied dwellings, representing 97% of Canadians. This analysis focused on children 6–11 years of age (n = 1080). Methods and results for children 6–19 years of age combined are presented elsewhere (Arbuckle et al., submitted). Information on child behavior, demographic, socioeconomic and lifestyle factors was collected by a questionnaire administered to the parent or guardian of these children.

2.2. Exposure assessment

Mid-stream urine and whole blood were collected, frozen and shipped to the Institut National de Santé Publique du Québec (http://www.inspq.qc.ca/ctqenglish/home) for analyses. Details on the lab's quality control and quality assurance measures and analytical methods are reported elsewhere (Health Canada, 2010). Blood was analysed for lead (limit of detection [LOD] 0.02 μg/dL), while urine was analysed for BPA (LOD 0.2 μg/L), cotinine (LOD 1.1 μg/L) and metabolites of di-n-butyl phthalate (mono-n-butyl phthalate [MBP] LOD 0.2 μg/L), diethyl phthalate (mono-ethyl phthalate [MEP] LOD 0.5 μg/L), dimethyl phthalate (mono-methyl phthalate [MMP] LOD 5 μg/L), butyl benzyl phthalate (mono-benzyl phthalate [MBzP] LOD 0.2 μg/L), di-cyclo-hexyl phthalate (mono-cyclo-hexyl phthalate [MCHP] LOD 0.2 μg/L), di-iso-nonyl phthalate (mono-isononyl phthalate [MNP] LOD 0.4 μg/L), di-n-octyl phthalate (mono-n-octyl phthalate [MOP LOD 0.7 μg/L], mono-(3-carboxypropyl) phthalate [MCPP] LOD 0.2 μg/L), and di-(2-ethylhexyl) phthalate (mono-(2-ethylhexyl) phthalate [MEHP] LOD 0.2 μg/L, mono-(2-ethyl-5-oxo-hexyl) phthalate [MEOHP] LOD 0.2 μg/L, mono-(2-ethyl-5-hydroxy-hexyl) phthalate [MEHHP] LOD 0.4 μg/L) using standardized methods (described in Arbuckle et al., 2014). Creatinine was measured to adjust for urine dilution using the colorimetric end-point Jaffe method. Any lab results below the limit of detection were imputed as half the limit of detection.

The administered questionnaire collected information on the child's current and prenatal exposure to environmental tobacco smoke (ETS).

2.3. Childhood behavior and development

The Strengths and Difficulties Questionnaire (SDQ) (www.sdqinfo.com) is a broad-band child mental health assessment tool that has been used in epidemiologic studies to screen for attention-deficit/hyperactivity disorder (ADHD) as well as other behavioral and emotional problems. The SDQ is highly correlated with other instruments such as the Child Behavior Checklist (Goodman and Scott, 1999).

The SDQ outcomes of interest for the multivariate analysis were emotional symptoms, hyperactivity/inattention, and the total difficulties score. Each sub-scale has validated cut-points where possible values for the SDQ variables are normal, borderline and abnormal. For the purposes of this analysis and to produce more reliable results in the multivariate models given the sample sizes, children with borderline and abnormal scores were grouped together and compared with children with normal scores for each of the scales and for the total difficulties scale.

Other outcomes studied included: parent-reported learning disability, and if yes, the type of learning disability: ADD or ADHD, dyslexia, or another type of learning disorder. Given the limited sample size, only any learning disability as well as ADD and ADHD combined were considered further. We also considered whether any medications used to treat behavioral disorders were taken in the past month. Respondents reported medications by Drug Identification Numbers (http://www.hc-sc.gc.ca/dhp-mps/prod-pharma/activit/fs-fi/dinfs_fd-eng.php) which were coded to Anatomical Therapeutic Chemical (ATC) codes (http://www.whocc.no/atc_ddd_index/). One of the co-authors (KB), a clinical child psychiatrist, provided a Table of medications potentially used for treating behavioral disorders in children (see Supplemental material, Table S1)

2.4. Statistical analysis

Initially, for each outcome of interest, univariate models were considered for each contaminant. Covariates identified through reviews of the literature included child's age, body mass index, number of hours slept per night, gender, highest level of household education (secondary school or less vs. at least some postsecondary studies), income adequacy (low/lower middle vs. upper middle/higher income), whether the child fasted prior to specimen collection, ETS exposure in the home, prenatal smoking, birth any time prior to due date (in response to the question: Was he born before, after or on the due date?), admission to a special neonatal unit or an intensive care unit prior to leaving hospital, and breast feeding (less than 3 months vs. three months or longer), as well as number of days in a neonatal unit, birth weight, and mother's age at birth. Based on preliminary modeling, lead was a significant covariate for most outcomes, and thus was included in models for BPA and phthalates.

Variables deemed significant at the 10% level in the univariate analysis were included in the multiple logistic regression models with the dichotomous outcomes as the dependent variable and individual natural log-transformed urinary concentrations as a predictor along with creatinine and lead. In order to determine which of the available predictor variables resulted in the best fit, a stepwise procedure was implemented whereby covariates were added to or removed from the model based on the relative significance and may or may not have remained in the model. For urinary chemicals, creatinine concentration was included in all the multiple regression models as a separate independent variable to correct for variable dilutions among spot urine samples. This approach allows the statistical significance of other variables in the model to be independent of effects of creatinine concentration (Barr et al., 2005).

Furthermore, since the CHMS employed a complex, multistage survey design, survey weights were used in descriptive statistics and statistical modeling to account for the unequal probabilities of selection. Due to the complex sampling scheme of the CHMS Cycle 1, direct calculation of standard errors and confidence intervals were not possible. To that end, Statistics Canada (2011) provided bootstrap weights in order to calculate standard errors, confidence intervals and coefficients of variation for each estimate using the bootstrap method.

Moreover, in a complex survey sampling design setting the degrees of freedom for statistical analysis are not related to the sample size; rather they are calculated based on the difference between the primary sampling units (or clusters) and the number of strata (Lohr, 2010). The CHMS Cycle 1 selected 15 primary sampling collection sites from a total of four regional strata, hence the degrees of freedom for statistical analysis is equal to (15–4) = 11. As a result of this reduced degrees of freedom, the CHMS Data User Guide (Statistics Canada, 2011) cautions to "avoid fitting models with a large number of coefficients."

In order to determine which of the available variables resulted in the best fit, a stepwise procedure was implemented. We considered the natural-log transformed contaminant and creatinine as *a priori* variables in the model. The natural-log of the contaminant concentrations was used since the contaminants were lognormally distributed based on the Anderson-Darling test. However since the complex survey design limited the number of degrees of freedom to 11, we employed a stepwise selection method to determine which covariates were most significant to improve the model fit. The contaminant and creatinine concentrations were retained in the model, and then other covariates were sequentially added to the model based on the smallest p-value (i.e. the most significant variables). This approach facilitated the evaluation of demographic variables one-at-a-time with respect to their p-value, conditional on other variables already in the model. This approach also served to examine the effect of multicollinearity, which could inflate standard errors and provide misleading results. For some models, after examining the main effects, sufficient degrees of freedom were available to evaluate an interaction term between highly significant covariates.

Furthermore, to compare models, we chose the model with significant terms and with the lowest value of the Akaike Information Criterion (AIC). We further assessed goodness of fit using the Hosmer-Lemeshow test. Model assumptions were also assessed as part of the regression fitting. Spearman correlations were calculated among the continuous covariates to assess

Table 1
Weighted proportion of individuals in the Canadian population with learning and SDQ outcome scores, CHMS Cycle 1 (2007–2009).

Age Group	Outcome	Sample size	Weighted Proportion (%)	95% Confidence Interval for Proportion
All Respondents (6–79 years of age)	Learning disability	276	3.64	2.97–4.31
	ADD	77	0.98	0.77–1.2
	ADHD	64	0.75 [E]	0.36 [E]–1.15 [E]
	Taking psychotropic medications	361	6.98	5.83–8.13
Children (6–11 years of age)	Learning disability	94	8.66	6.71–10.61
	ADD	20	1.48[E]	0.58[E]–2.38[E]
	ADHD	29	2.75[E]	0.82[E]–4.68[E]
	Taking psychotropic medications	42	3.65[E]	2.09[E]–5.21[E]
	SDQ Conduct problems	165	15.28	11.85–18.72
	SDQ Hyperactivity/inattention	182	16.88	14.10–19.67
	SDQ Emotional symptoms	166	14.98	13.51–16.45
	SDQ Peer relationship problems	147	13.42	10.03–16.80
	SDQ Pro-social behavior	26	2.73[E]	1.10[E]–4.36[E]
	SDQ Total difficulties	128	13.01	10.31–15.71

E, Warning that high sampling variability is associated with these estimates. Results should be interpreted with caution. ($16.6\% \leq CV \leq 33.3\%$).

Table 2
Weighted Pearson correlation coefficients of SDQ outcome scores from CHMS Cycle 1 (2007–2009) for children 6–11 years.

SDQ Scale	Conduct problems	Emotional symptoms	Hyperactivity/ inattention	Pro-social behavior	Peer-relationship problems	Total Difficulties
Conduct problems	1	0.2544	0.5831	−0.4572	0.3397	0.7303
Emotional symptoms		1	0.3158	−0.0739	0.3383	0.6420
Hyperactivity/inattention			1	−0.3193	0.3804	0.8452
Pro-social behavior				1	−0.2713	−0.3779
Peer-relationship problems					1	0.6674
Total Difficulties						1

potential multicollinearity. When associations were noted between covariates, separate models were fit for each variable to reduce the effects of multicollinearity. Important in the modeling of survey data, we also assessed the informativeness of the sampling design (Binder et al., 2005; Lohr, 2010).

The software package SAS (Statistical Analysis System) Enterprise Guide 4.2 was used for statistical analysis. For both descriptive statistics and regression modeling, the software programs BOOTVAR and SUDAAN were used along with the bootstrap weights, in order to correctly calculate such estimates. Finally, for all statistical analysis performed, an inference was deemed significant at $\alpha = 5\%$ unless otherwise indicated.

3. Results

3.1. Prevalence of developmental difficulties

Table 1 provides the weighted proportion of individuals in the Canadian population with developmental and behavioral outcomes of interest. Based on parental reports, the prevalence of a learning disability, ADD, and ADHD in children 6–11 years of age was 8.7%, 1.5% and 2.8%, respectively. The ADD/ADHD outcomes represented about half of all the learning disabilities reported. In the same age group, based on SDQ scores, the prevalence for hyperactivity/inattention, emotional symptoms and total difficulties was 16.9%, 15.0% and 13.0%, respectively. Most SDQ scores were positively correlated with the exception of scores related to pro-social behavior, which were negatively correlated with other SDQ outcomes (Table 2). Sample sizes were too small to exclude children taking psychotropic medications from analysis of the other outcomes. There were many children who were treated with psychotropic medications yet still had reported learning/SDQ outcomes. For instance, considering the unweighted frequencies, there were 49 children aged 6–11 who were reported as having ADD/ADHD, of whom 29 were taking psychotropic medications and 20 who were not.

3.2. Prevalence of environmental exposures

The weighted descriptive statistics for BPA, cotinine, phthalates and lead are presented in Table 3 and compared with those from the US NHANES (CDC, 2014). The geometric means for children 6–

Table 3
Comparison of Canadian and US statistics for environmental chemical concentrations in urine and lead in blood for children, CHMS Cycle 1 (2007–2009) (Health Canada, 2010) and NHANES (2007–2008) (CDC, 2014).

Chemical	Age	Survey	N	% <LOD	GM	95th Percentile
Bisphenol A (μg/L)	6–11	CHMS	1038	6.44[E]	1.31	7.24
		NHANES	389		2.48	13.4
Cotinine (μg/L)[a]	6–11	CHMS	1052	84.06	0.81	10.28
Phthalates (μg/L)						
MBzP	6–11	CHMS	1044	0.00	21.23	131.08
		NHANES	389		15.4	131
MBP	6–11	CHMS	1044	0.00	33.11	167.19
		NHANES	389		26.9	119
MCHP	6–11	CHMS	1044	84.40	<LOD	F
		NHANES	389		X	<LOD
MEP	6–11	CHMS	1044	F	26.06	210.64[E]
		NHANES	389		49.0	296
MEHP	6–11	CHMS	1044	0.00	3.33	17.76
		NHANES	389		2.39	15.1
MEHHP	6–11	CHMS	1044	0.00	31.54	179.53
		NHANES	389		28.6	242
MEOHP	6–11	CHMS	1044	0.00	19.99	106.66
		NHANES	389		16.9	137
MOP	6–11	CHMS	1044	95.47	<LOD	F
		NHANES	389		X	<LOD
MMP	6–11	CHMS	1044	66.12	<LOD	24.53
		NHANES	389		X	12.1
MCPP	6–11	CHMS	1044	2.66[E]	2.67	13.39
		NHANES	389		6.01	23.9
MNP	6–11	CHMS	1043	99.16	<LOD	<LOD
		NHANES	389		X	2.16
Lead (μg/dL)	6–11	CHMS	915	0.00	0.90	1.96
		NHANES	1011		0.988	2.50

GM: geometric mean; LOD: limit of detection; X: not calculated as proportion below detection limit too high; E: Warning that high sampling variability is associated with these estimates. Results should be interpreted with caution. ($16.6\% \leq CV \leq 33.3\%$); F: these estimates are of unacceptable quality, as determined by Statistics Canada release guidelines and are suppressed.

[a] NHANES measures serum rather than urinary cotinine concentrations.

Table 4
Weighted Descriptive Statistics for Socio-Demographic Covariates of Interest for Children Ages 6–11 years: CHMS Cycle 1 (2007–2009).

Variable	n	Arithmetic Mean	95% Confidence Interval	
Child's Age	1080	8.58	8.38	8.79
No. of hours slept	1080	9.68	9.57	9.79
Birth weight (g)	1045	3395.10	3337.30	3452.89
BMI	1078	17.80	17.55	18.04
Mother's age at birth	1071	29.15	28.44	29.87

Variable	n	Percent	95% Confidence Interval	
Males	547	51.2%	51.0	51.4
Canadian-born	982	92.3%	86.0	98.5
Prenatal smoking (Yes)	163	17.1%	13.1	21.2
Smoking at home (Yes)	122	10.3%	7.4	13.3
Low birth weight (Yes)	66	5.7%	3.9	7.4
Special neonatal unit care (Yes)	153	12.8%	9.3	16.2
Born any time before due date (Yes)	440	41.8%	37.4	46.2
Breastfed > = 3 months	862	83.4%	79.7	87.1
Fasted (Yes)	556	50.3%	46.4	54.2
Household Income: Low/Low-middle	267	26.7%	20.0	33.4
Highest Level of Education: High School or less	134	13.0%	9.2	16.8

11 years old were 1.3, 21.2, 33.1 and 31.5 μg/L for BPA, MBzP, MBP, and MEHHP, respectively and 0.9 μg/dL for lead. It was evident that, for some contaminants, both unadjusted and creatinine-adjusted BPA and phthalate urinary concentrations in the children differed by age, gender and exposure to prenatal smoking (data not shown). Regression modeling was used to further analyze these differences while accounting for other demographic variables of interest. Cotinine and the phthalates MCHP, MMP, MNP and MOP were not considered further since more than 65% of the data fell below the limit of detection, and statistical reliability was questionable.

3.3. Descriptive statistics of covariates of interest

Table 4 provides summary statistics for covariates considered in the analysis. We note that the average age of children in this study was 8.58 years (95% CI 8.38–8.79) with average maternal age at birth of 29.15 years (95% CI 28.4–29.9). Furthermore, 51.2% of the children were males, while 92.3% were born in Canada. Further, 10.3% reported smoking at home (95% CI 7.4–13.3%) while 17.1% reported prenatal smoking (95% CI 13.1–21.2%). We also note that 12.8% of children required neonatal unit care, 41.8% were born any time prior to their due date and 83.4% of mothers breastfed for more than 3 months.

3.4. Multivariate analysis: environmental chemicals

Odds ratios calculated from weighted multiple logistic regression models are presented for the reported (Table 5) and the SDQ (Table 6) identified outcomes. Models are presented in the Supplemental materials.

Blood lead was statistically (p = 0.047) associated with reported ADD/ADHD in the weighted multiple regression model. A 1-unit increase in ln-blood lead increased the odds of ADD/ADHD by 2.08 (95% CI = 1.01–4.25), other variables held constant (Table 5 and Supplemental material Table S2). The nature of the association between ln-MEHP and ADD/ADHD depended on the child's gender, with increasing ln-MEHP associated with a significantly lower risk of ADD/ADHD in females (OR: 0.25; 95% CI 0.11–0.57).

None of the contaminants were significantly associated with reported learning disability (Supplemental material Table S3). BPA and lead were significantly associated with taking psychotropic medication (ln-BPA: OR = 1.59; 95% CI 1.05–2.40 and ln-Lead: OR = 2.91, 95% CI 1.47–5.79) (Table 5 and Supplemental material Table S4).

In regards to the SDQ outcomes, the only contaminant associated with the total difficulties score was lead and a significant interaction term between lead and prenatal smoking (p = 0.029) was observed. Specifically, for each one unit increase in

Table 5
Summary of Multiple Logistic Regression Results for Parent-Reported Outcomes from the Canadian Health Measures Survey Cycle 1 (Weighted) for Children Aged 6–11 Years.

Contaminant	ADD/ADHD OR (95% CI)	Any Learning Disability OR (95% CI)	Psychotropic Medicine Taken OR (95% CI)
BPA	1.31 (0.81–2.12)	1.31 (0.89–1.92)	1.59 (1.05–2.40)
MBP	0.62 (0.34–1.15)	0.94 (0.61–1.46)	0.63 (0.28–1.42)
MBzP	1.41 (0.94–2.13)	1.57 (0.89–2.79)	0.92 (0.49–1.70)
MCPP	1.32 (0.69–2.51)	1.30 (0.86–1.98)	1.28 (0.67–2.42)
MEHHP	0.72 (0.29–1.78)	0.84 (0.42–1.68)	1.08 (0.28–4.20)
MEHP	M: 0.96 (0.53–1.76) F: 0.25 (0.11–0.57)[a]	0.88 (0.50–1.54)	1.02 (0.26–4.04)
MEOHP	0.66 (0.20–2.10)	0.84 (0.37–1.94)	1.05 (0.25–4.36)
MEP	0.83 (0.44–1.57)	1.00 (0.47–2.14)	1.41 (0.63–3.18)
Blood Lead	2.08 (1.01–4.25)	1.41 (0.73–2.70)	2.91 (1.47–5.79)

M: males; F: females. Models adjusted for covariates as determined by a stepwise multiple regression procedure (see Supplemental material).
[a] Interaction terms significant at 5% level between contaminant and other covariates.

Table 6
Summary of Multiple Regression Results for SDQ outcome scores from the Canadian Health Measures Survey Cycle 1 (Weighted) for Children Aged 6–11 Years.

Contaminant	Total Difficulties OR (95% CI)	Emotional Symptoms OR (95% CI)	Hyperactivity/Inattention OR (95% CI)
BPA	1.01 (0.73–1.41)	1.02 (0.85–1.23)	1.05 (0.84–1.30)
MBP	PS: 2.34 (0.81–6.78) NPS: 0.85 (0.73–1.00)	0.79 (0.58–1.08)	1.05 (0.64–1.74)
MBzP	1.26 (0.96–1.66)	M: 1.05 (0.82–1.36) F: 1.38 (1.09–1.75)[a]	1.05 (0.78–1.41)
MCPP	1.21 (0.77–1.89)	0.96 (0.78–1.19)	1.30 (1.00–1.70)
MEHHP	1.00 (0.60–1.65)	0.87 (0.59–1.29)	1.02 (0.61–1.70)
MEHP	1.11 (0.57–2.15)	0.86 (0.65–1.15)	0.96 (0.57–1.64)
MEOHP	0.99 (0.59–1.64)	0.86 (0.60–1.22)	0.96 (0.56–1.66)
MEP	1.16 (0.86–1.58)	1.05 (0.73–1.51)	1.12 (0.94–1.33)
Blood Lead	PS: 10.57 (2.81–39.69) NPS: 1.98 (1.41–2.79)[a]	1.25 (0.60–2.59)	2.75 (1.46–5.16)

PS: prenatal smoking; NPS: no prenatal smoking. Models adjusted for covariates as determined by a stepwise multiple regression procedure (see Supplemental material).
[a] Interaction terms significant at 5% level between contaminant and other covariates.

the ln-lead level, the odds ratio for a borderline/abnormal total difficulties score was higher if their mother smoked during pregnancy than for children whose mother did not smoke (ln-lead: prenatal smoking OR = 10.57; 95% CI 2.81–39.69 vs. no prenatal smoking OR = 1.98; 95% CI 1.41–2.79) (Table 6 and Supplemental material Table S7).

For the emotional symptoms score, only MBzP ($p = 0.046$) was significant and varied by gender. A higher odds ratio was noted for females than males (ln-MBzP: females OR = 1.38; 95% CI 1.09–1.75 vs. males OR = 1.05, 95% CI 0.82–1.36). (Table 6 and Supplemental material Table S5).

Weighted regression models showed that only blood lead was significantly associated ($p = 0.005$) with hyperactivity/inattention SDQ outcome (Supplemental material Table S6). A one unit increase in ln-lead was associated with an odds ratio of 2.75 (95% CI 1.46–5.16).

Prenatal smoking was a significant factor for many outcomes, including ADD/ADHD, presence of a learning disability, SDQ hyperactivity/inattention and SDQ total difficulties (see Supplemental material tables).

3.5. Multivariate analysis: other covariates

In the course of analysis, other covariates not of primary research interest were found to be significant using weighted multiple logistic regressions. Gender was significantly associated with many outcomes, with males generally at higher risk than females. A notable exception was SDQ emotional symptoms, where the odds ratio for females was higher than that for males (Supplemental material Table S5).

Breastfeeding was significant for some models of the outcome SDQ hyperactivity/inattention (Supplemental material Table S6). In several models, the interaction term between breastfeeding and gender was significant. For example, males breastfed for 3 or more months had an odds ratio for hyperactivity/inattention of 0.35 (95% CI = 0.19–0.65) compared to males who were breastfed less than 3 months. For females, breastfeeding did not significantly impact the odds of hyperactivity/inattention (OR = 1.14, 95% CI = 0.65–2.02).

The number of hours slept per night had a negative and significant association with the presence of a learning disability, SDQ emotional symptoms, SDQ hyperactivity/inattention, and SDQ total difficulties. As an example, one additional hour of sleep for 6–11 year old children was associated with a decrease in the odds of a total difficulty problem by 0.54 (95% CI = 0.37–0.78) (Supplemental material Table S7).

Further, the child's age was significantly and positively associated with reported learning disability (Supplemental material Table S3).

Finally, birth any time prior to due date was significantly associated with reported ADD/ADHD, taking psychotropic medications, SDQ emotional symptoms, and SDQ total difficulties (Supplemental material). For instance, the odds of having a total difficulties score was 2.11 times higher for a child born prior to due date versus a birth at or after the due date (95% CI = 1.10–4.03), other variables held constant (Supplemental material Table S7).

In terms of model fit, some of the weighted models presented exhibited minor lack of fit, in that results of the Hosmer-Lemeshow test often exhibited p-values near 0.10, and some large residuals were noted. Transformations were considered, such as higher-order terms (quadratic, cubic, etc.) to consider nonlinear relationships and improve model fit; however, only slight improvements were noted. Unfortunately other remedial measures could not be considered since the CHMS sample design prescribed only 11 degrees of freedom for hypothesis testing; hence additional variables could not be included and tested within the model.

4. Discussion

Recent reviews have shown that environmental chemicals may play a role in the etiology of behavioral and developmental disorders (Grandjean and Landrigan, 2014; Rochester, 2013; Jurewicz et al., 2013; Braun et al., 2013). In our study, the results indicated that environmental chemicals such as lead and to a lesser extent BPA and some phthalates may be associated with behavioral problems among Canadian children.

We found that lead was the environmental chemical most often associated with a variety of non-internalizing behavioral outcomes, even after controlling for variables such as smoking, gender, breastfeeding and household income. There was some internal consistency in the results in that lead was associated with increased risks of ADD/ADHD, taking psychotropic medications, as well as SDQ hyperactivity/inattention and total difficulties scores. We found a significant interaction between child blood lead and prenatal ETS exposure for the total difficulties score (OR 10.57; 95% CI 2.81–39.69); although the confidence interval was large and only seventeen percent of the children were prenatally exposed to ETS. Froehlich et al. (2009) also found that children with both prenatal ETS and 3rd tercile blood lead levels (>1.3 μg/dL) had an OR of 8.1 (95% CI 3.5–18.7) for ADHD. Higher blood lead concentration in children has been associated with conduct disorders in the US NHANES (Braun et al., 2008), as well as

hyperactivity and impulsivity symptoms in Korea (Hong et al., 2015) even after adjusting for multiple confounding variables. Although blood lead concentrations have decreased over the past decades, new research on lead has demonstrated that its toxicity has not disappeared and that a threshold level below which lead can be considered "safe" has yet to be identified (Bellinger, 2011). It has been estimated that the impact of lead exposure on Full-Scale IQ (FSIQ) scores of children less than 5 years of age is a loss of 23,000,000 points, compared to a loss of 34,000,000 FSIQ points for a major non-chemical risk factor such as preterm birth (Bellinger, 2012). Decreasing lead exposure in children must continue to be a major public health priority, and in particular for the reduction of risk for behavioural difficulties in children.

We found that exposure to BPA was associated with taking medications for behavioral problems in boys and girls, but not behavioural or emotional problems, themselves. However, in another cross-sectional study of child exposure to BPA and behavior that also adjusted for phthalates and lead exposure, urinary BPA was positively associated with the Child Behavior Checklist (CBCL) Total Problems score (Hong et al., 2013). BPA concentrations appeared to be similar in the two surveys.

Considering studies which have sampled children in the same age range used in our analysis, higher post-natal BPA was associated with increased behaviors on both the CBCL internalizing, composite, and externalizing composite scores and individual subscores in girls only (Roen et al., 2015), or boys only (Harley et al., 2013) with conduct symptoms being the only symptom for exposure in girls (Harley et al., 2013).

Although there is some inconsistency in the literature which might be related to the use of different tools to assess children's behavior, it appears that the timing of exposure to BPA may have a significant impact on gender differences in the relationship between BPA and neurobehavioral functions. While the two cross-sectional studies (current study; Hong et al., 2013) did not report any gender-dependent effects for BPA, two cohort studies of post-natal exposure found associations predominantly in girls (Harley et al., 2013; Roen et al., 2015). In contrast, prenatal exposure to BPA was associated with increased behavioral problems in boys in most of the studies (Perera et al., 2012; Evans et al., 2014; Harley et al., 2013; Roen et al., 2015), with one exception where more adverse effects were observed in girls (Braun et al., 2009, 2011). A recent review has also reported stronger associations between prenatal vs. childhood exposure to BPA and adverse behavioral effects in six out of seven studies examined (Mustieles et al., 2015).

The animal literature suggests that exposure to BPA affects the development of the forebrain dopaminergic system via binding to estrogen dependent dopaminergic receptors that are important for regulation of behavioral impulses (Narita et al., 2006; Suzuki et al., 2003). Forebrain regions are also important for controlling emotional regulation and reactivity, a neurobehavioral function that may be measured in the rating scales various studies have used. Prior to puberty, the risk for most behavioural outcomes and in some cases emotional outcomes is greater for boys. This risk may be related to relative immaturity of the forebrain regions in boys (Neufang et al., 2009). The apparent endocrine profile produced by BPA is an elevation of serum T4 despite normal TSH levels and an apparent overstimulation of the TRα receptor (Zoeller, 2006). This profile is similar to that in humans caused by a mutation in the TRβ receptor with the subsequent thyroid resistance syndrome (Refetoff et al., 1994) which was found to be associated with a number of symptoms including attention deficit disorders (Cheng, 2005; Togashi et al., 2005). BPA exposure also induces prefrontal and hippocampal spine synapse loss in rodents which may result in cognitive dysfunction and developmental depressive behavior (Hajszan and Leranth, 2010). A key finding across a range of developmental toxicity studies is that BPA has shown effects on sex-differentiation of exploratory and affective behavior at lower doses (Golub et al., 2010). There is also some evidence to suggest that BPA can result in changes in structural development of the brain, disruption of estrogen regulation at a number of levels, alterations in DNA methylation of the genome, and affect social behavior, anxiety and maternal behavior (Wolstenholme et al., 2011). Thus, BPA is associated with behavioral syndromes in rats in laboratory conditions possibly as the result of BPA interference with hormonal and genomic regulation and brain neurogenesis. Whether these effects occur in humans at typical environmental exposure levels is unknown, although if they occur, it is likely that the effects are sex dependent in their expression given the observed sex differences in developmental brain physiology that have been reported.

Among the phthalate metabolites, MCPP was associated with higher odds of SDQ hyperactivity/inattention (1.30, 95% CI 1.00–1.70). In contrast, an analysis of the US NHANES data for children 6–15 years of age reported no significant association of MCPP with learning difficulties or ADD (Chopra et al., 2014). It should be noted that MCPP is a non-specific metabolite of multiple parent phthalates.

MBzP was associated with higher odds of SDQ emotional symptoms in girls, but no other outcomes. In a cross-sectional analysis in the US, MBzP was also not associated with ADD or a learning disability (Chopra et al., 2014). However, two studies of prenatal exposure to MBzP have reported associations with internalizing behaviors in girls (Whyatt et al., 2012; Kobrosly et al., 2014). MBzP is the major metabolite of benzylbutyl phthalate, which is used in Canada as a plasticizer in polyvinyl chloride (PVC) flooring and other materials, in paints and coatings, in adhesive formulations and in printing inks (Health Canada and Environment Canada, 2000).

Our observations that increasing urinary concentrations of MEHP (a DEHP metabolite) in children 6–11 years of age was associated with a significantly decreased risk of ADD/ADHD and was not associated with SDQ hyperactivity/inattention are not consistent with previous studies which in general report an increased risk of ADHD symptoms (Kim et al., 2009; Park et al., 2015). However, an analysis of US NHANES (2001–2004) for children 6–15 years of age reported an increased odds of parent-reported ADD with increasing urinary DEHP and high molecular weight phthalates, with stronger associations observed in girls than boys (Chopra et al., 2014). A recent systematic review further suggested that elevated prenatal exposure to phthalate metabolites was also associated with poorer cognitive and behavioral outcomes in children less than 12 years of age with gender-specific differences observed, but also identified a number of inconsistencies in the literature (Ejaredar et al., 2015). A number of factors may explain the inconsistencies among these studies: the diverse cognitive and behavioral functions assessed as well as the use of different tools to measure these functions, different levels of exposure among the studies, the potential exposure misclassification introduced by using a single urine void to measure exposure (Fisher et al., 2015), varying mixtures of phthalates, the timing of the exposure measure, and the genetic make-up of the populations, as well as other unknown factors.

Based on the results of studies of prenatal exposure to phthalates and poor performance on neurodevelopmental test scores, the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives has recommended that human exposure to DEHP, DBP and DEP should be reduced (US Consumer Product Safety Commission, 2014).

As with BPA, the biological mechanisms underlying any potential associations between phthalates and child behavior are still to be determined. There are published reports of

associations between phthalates and altered thyroid hormones. Thyroid hormones play a critical role in fetal and child growth and brain development (Diamanti-Kandarakis et al., 2009). In a cross-sectional analysis of NHANES data, inverse relationships between urinary metabolites of DEHP and total T4 levels were observed in adult participants (Meeker and Ferguson, 2011). In contrast, in participants 12–19 years, there was evidence of a positive relationship between DEHP metabolites and T3 and TSH. However, a Danish study of children 4–9 years reported an inverse relationship between DEHP metabolites and free and total T3 (Boas et al., 2010). A small study (n = 76) of pregnant women reported a significant inverse association between urinary MnBP and serum levels of free and total T4 (Huang et al., 2007). As the correlations between phthalate exposure and thyroid indicators are different, although not necessarily inconsistent across these differently aged populations, the impact of phthalates on thyroid function is likely to be developmental and requires further investigation.

Consistent with previous research, prenatal but not post-natal exposure to tobacco was significantly associated with various child behavioral outcomes in this analysis. Prenatal ETS exposure has been more consistently predictive of ADHD than postnatal exposures (Braun et al., 2006).

Our results showed that the number of hours slept per night was negatively associated with whether psychotropic medications were taken and various SDQ scales. Child sleep problems are a prominent clinical comorbidity with ADHD (Owens et al., 2013) and significantly associated with poorer academic, behavioral and social functioning (Becker, 2014).

Given that being born any time before anticipated due date was such an important developmental factor associated with psychopathology/behavioral problems in our analysis of children 6–11 years of age, we recommend that this factor be considered in multivariate models in future research to examine risk factors for these outcomes.

5. Strengths and limitations

A strength of this exploratory analysis is that, as the CHMS is a large biomonitoring survey representative of the Canadian population, we were able to generalize these results, using weighted estimates, to the Canadian population 6–11 years of age. In addition, we were able to consider statistical interactions with a number of critical factors including co-exposure to lead.

There are a number of limitations to this analysis that preclude any conclusions about etiology; key amongst these is the cross-sectional nature, which does not allow a time interval between exposure and disease onset. Therefore, it is also possible that children experiencing adverse behaviors such as ADHD are at higher risk of greater exposure to environmental lead (Goodlad et al., 2013) and possibly other chemicals.

There were several important potential risk factors that we could not include in our analyses such as measures of maternal nutrition and mental health. A recent study reported that higher maternal circulating levels of 25(OH)D3 in pregnancy were associated with lower risk of developing ADHD-like symptoms in childhood (Morales et al., 2015). We also could not adjust for a set of robust contextual and biological confounding variables to children's learning and behavioral outcomes, namely parental learning and behavioral indicators. Approximately 75% of the etiologic processes contributing to ADHD are genetic in origin (Biederman and Faraone, 2005) while the heritability of other psychiatric disorders is also substantial (between 30 and 60% on average). Further, we could not control for factors that might affect the reported outcomes such as the child's family relationships including experience of abuse, neglect, or witnessing violence in the home.

A major limitation of this analysis is the likely exposure misclassification bias due to the short elimination half-life of BPA and phthalates. There can be considerable intra-individual variability in urinary concentrations of BPA (Heffernan et al., 2014) and phthalates (Teitelbaum et al., 2008; Watkins et al., 2014) in children. In pregnant women, BPA and phthalates measured in urine have shown considerable variability within a day and across days, with low sensitivity to correctly classify a single sample as high or low exposure (Fisher et al., 2015). Depending on the sources of exposure, when the urine was collected can also have a significant impact on the urinary concentration measured.

Children are exposed to combinations of chemicals that may exert additive, synergistic or antagonistic effects on neurodevelopment. Our limited sample size did not permit examination of mixtures of a broad range of potential neurotoxicants.

Some of the estimated rates of the outcomes studied were subject to high sampling variability (Table 1) and therefore these results should be interpreted with caution. Furthermore, the outcomes of interest were based on answers to survey questions by respondents and may be subject to reporting bias. Recall bias may also occur as parents may not remember certain details surrounding their habits during a pregnancy that occurred several years ago, or may fail to report exposure to certain factors such as prenatal smoking or breastfeeding, due to social stigma.

As multiple analyses were conducted, significant results may have been found by chance. Finally, contaminant levels which were below the laboratory's limit of detection, i.e. non-detects, were substituted by half of the value of the limit of detection, prior to statistical analysis. Recent research has indicated that in the unweighted setting, such substitution may lead to biased and inefficient estimates, compared to other techniques such as maximum likelihood methods (Helsel, 2012). However, little research is available on analysis of complex survey data in the presence of non-detects, thus future work which would extend such models to design-based estimates would be advantageous.

6. Conclusions

Our findings on postnatal exposures and emotional and behavioural outcomes in children are generally consistent with the existing literature; however, some differences are notable such as the absence of an association between DEHP phthalate metabolites and ADHD or behavioural outcomes that has been observed in other studies (Kim et al., 2009; Testa et al., 2012; Chopra et al., 2014; Park et al., 2015). In fact, we observed a significantly lower risk of ADD/ADHD in girls with increasing MEHP levels. We also observed an association between MCPP and ADHD which has not been previously reported. The association between BPA and prescriptions for behaviour disorders suggests an association between BPA and behaviour disorders or attention problems as supported robustly in the literature even though the measure is indirect.

There are also important sex differences in the strength and direction of the associations between chemical exposures and behavioural or emotional outcomes in children, but we only demonstrated the increased risk of emotional symptom in girls in association with MBzP. The absence of replication of others' findings of sex differences may be because of the reduced number of items the SDQ contains to measure these domains compared to more commonly used measures (CBCL) in other studies. Sex differences in ADHD would be difficult to detect as ADHD in girls is typically under-identified in studies where parent and teacher self-report measures are used (Quinn, 2008).

Despite evidence for the psychometric distinction of emotional and behavioural problems, and aspects of their distinct etiological processes, it is important to recognize that there is significant common variance amongst these domains. Comorbidity and correlation is common (average correlation estimate at 0.4) (Krueger et al., 2001). The finding of specificity of exposures to one versus the other outcome is important and suggests important differences in mechanisms by which environmental chemicals affect the development of psychological symptoms. Indeed, further characterization and measurement of processes such as thyroid metabolism and brain imaging in relation to environmental exposures at different developmental stages will help establish the mechanism of risk relevant to such exposure.

In conclusion, our results indicated that environmental chemicals such as lead and prenatal exposure to environmental tobacco smoke were associated with learning disabilities and behavioral problems. Lead was significantly associated with reported ADD/ADHD and SDQ hyperactivity/inattention and total difficulties. Furthermore, the association between lead and SDQ total difficulties was significantly increased in children who were prenatally exposed to tobacco. To a lesser extent, BPA and a few phthalates were associated with some behavioral outcomes; however it is unlikely that having only a single concurrent and unreliable measure of these chemicals captured the pertinent exposures for chronic conditions such as ADHD. The child's gender, age, hours of sleep, birth any time prior to due date, stay in a special neonatal unit after birth, breastfeeding and prenatal exposure to ETS were often important covariates in the various models.

While the study did examine multiple environmental risk factors, the cross-sectional nature of the study limited our ability to conclude that exposure to environmental chemicals was causally linked with adverse child behaviors. These findings underscore the need for prospective cohort studies measuring different combinations of environmental chemicals in concert with key child neurodevelopmental risk factors for such outcomes to better elucidate the etiology of ADHD and other child learning and behavioral problems. Future studies of non-persistent chemicals such as BPA need to develop more accurate measures of exposure. Given the high costs of collecting and analysing multiple samples per individual, research should focus on developing statistical models that take into account predictors of urinary concentrations such as time of day, time since last void, weekday vs weekend, intra-class correlation coefficients for the time period of interest and hydration status (Arbuckle et al., 2015; Fisher et al., 2015).

Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neuro.2016.03.014.

References

Abbott, L.C., Winzer-Serhan, U.H., 2012. Smoking during pregnancy: lessons learned from epidemiological studies and experimental studies using animal models. Crit. Rev. Toxicol. 42 (April (4)), 279–303.

Arbuckle, T.E., Davis, K., Marro, L., Fisher, M., Legrand, M., LeBlanc, A., Gaudreau, E., Foster, W.G., Choeurng, V., Fraser, W.D., 2014. MIREC Study Group. Phthalate and bisphenol A exposure among pregnant women in Canada-results from the MIREC study. Environ. Int. 68 (July), 55–65. doi:http://dx.doi.org/10.1016/j.envint.2014.02.010 (Epub 2014 Apr 4).

Arbuckle, T.E., Weiss, L., Fisher, M., Hauser, R., Dumas, P., Bérubé, R., Neisa, A., LeBlanc, A., Lang, C., Ayotte, P., Walker, M., Feeley, M., Koniecki, D., Tawagi, G., 2015. Maternal and infant exposure to environmental phenols as measured in multiple biological matrices. Sci. Total Environ. 508 (March), 575–584. doi:http://dx.doi.org/10.1016/j.scitotenv.2014.10.107 (Epub 2014 Dec 4).

Arbuckle, T.E., Davis, K., Boylan, K., Fisher, M., Fu, J. BPA, Phthalates and Lead and Learning and Behavioral Problems in Canadian Children 6–19 years of age: CHMS 2007–2009. Data in Brief (submitted).

Barr, D.B., Wilder, L.C., Caudill, S.P., Gonzalez, A.J., Needham, L.L., Pirkle, J.L., 2005. Urinary creatinine concentrations in the U.S. populations: implications for urinary biologic monitoring measurements. Environ. Health Perspect. 113, 192–200.

Becker, K., El-Faddagh, M., Schmidt, M.H., Esser, G., Laucht, M., 2008. Interaction of dopamine transporter genotype with prenatal smoke exposure on ADHD symptoms. J. Pediatr. 152 (February (2)), 263–269.

Becker, S.P., 2014. External validity of children's self-reported sleep functioning: associations with academic, social, and behavioral adjustment. Sleep Med. 15 (September (9)) doi:http://dx.doi.org/10.1016/j.sleep.2014.06.001 (1094-100 Epub 2014 Jun 9).

Bellanger, M., Demeneix, B., Grandjean, P., Zoeller, R.T., Trasande, L., 2015. Neurobehavioral deficits, diseases, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. J. Clin. Endocrinol. Metab. 100 (April (4)), 1256–1266. doi:http://dx.doi.org/10.1210/jc.2014-4323.

Bellinger, D.C., 2011. The protean toxicities of lead: new chapters in a familiar story. Int. J. Environ. Res. Public Health 8 (July (7)), 2593–2628.

Bellinger, D.C., 2012. Comparing the population neurodevelopmental burdens associated with children's exposures to environmental chemicals and other risk factors. Neurotoxicology 33 (August (4)), 641–643.

Biederman, J., Faraone, S.V., 2005. Attention-deficit hyperactivity disorder. Lancet 366 (July (9481)), 237–248.

Binder, D.A., Kovacevic, M.S., Roberts, G., 2005. Impact of informativeness of the sample design on statistical inference. Proceedings of Statistics Canada Symposium 2005: Methodological Challenges for Future Information Needs (Catalogue no. 11-522-XIE).

Boas, M., Frederiksen, H., Feldt-Rasmussen, U., Skakkebæk, N.E., Hegedüs, L., Hilsted, L., Juul, A., Main, K.M., 2010. Childhood exposure to phthalates: associations with thyroid function, insulin-like growth factor I, and growth. Environ. Health Perspect. 118 (October (10)), 1458–1464.

Boyle, C.A., Boulet, S., Schieve, L.A., Cohen, R.A., Blumberg, S.J., Yeargin-Allsopp, M., Visser, S., Kogan, M.D., 2011. Trends in the prevalence of developmental disabililties in US children, 1997–2008. Pediatrics 127 (6), 1034–1042.

Braun, J.M., Kahn, R.S., Froehlich, T., Auinger, P., Lanphear, B.P., 2006. Exposure to environmental toxicants and attention deficit hyperactivity disorder in U. S. children. Environ. Health Perspect. 114, 1904–1909.

Braun, J.M., Froehlich, T.E., Daniels, J.L., Dietrich, K.N., Hornung, R., Auinger, P., Lanphear, B.P., 2008. Association of environmental toxicants and conduct disorder in U.S. children: NHANES 2001–2004. Environ. Health Perspect. 116 (July (7)), 956–962.

Braun, J.M., Yolton, K., Dietrich, K.N., Hornung, R., Ye, X., Calafat, A.M., Lanphear, B.P., 2009. Prenatal bisphenol A exposure and early childhood behavior. Environ. Health Perspect. 117 (December (12)), 1945–1952.

Braun, J.M., Kalkbrenner, A.E., Calafat, A.M., Yolton, K., Ye, X., Dietrich, K.N., Lanphear, B.P., 2011. Impact of early-life bisphenol A exposure on behaviour and executive function in children. Pediatrics 128 (November (5)), 873–882.

Braun, J.M., Sathyanarayana, S., Hauser, R., 2013. Phthalate exposure and children's health. Curr. Opin. Pediatr. 25 (April (2)), 247–254.

CDC, 2014. Fourth National Report on Human Exposure to Environmental Chemicals. Department of Health and Human Services, Centers for Disease Control and Prevention (Updated Tables, August).

Cheng, S.Y., 2005. Thyroid hormone receptor mutations and disease: beyond thyroid hormone resistance. Trends Endocrinol. Metab. 16 (May–June (4)), 176–182.

Chopra, V., Harley, K., Lahiff, M., Eskenazi, B., 2014. Association between phthalates and attention deficit disorder and learning disability in U.S. children, 6–15 years. Environ. Res. 128 (January), 64–69.

Copeland, W.E., Miller-Johnson, S., Keeler, G., Angold, A., Costello, E.J., 2007. Childhood psychiatric disorders and young adult crime: a prospective, population-based study. Am. J. Psychiatry 164 (November (11)), 1668–1675.

Copeland, W.E., Adair, C.E., Smetanin, P., Stiff, D., Briante, C., Colman, I., Fergusson, D., Horwood, J., Poulton, R., Costello, E.J., Angold, A., 2013. Diagnostic transitions from childhood to adolescence to early adulthood. J. Child Psychol. Psychiatry 54 (July (7)), 791–799.

Dalsgaard, S., Mortensen, P.B., Frydenberg, M., Thomsen, P.H., 2013. Long-term criminal outcome of children with attention deficit hyperactivity disorder. Crim. Behav. Ment. Health 23 (April (2)), 86–98.

Diamanti-Kandarakis, E., Bourguignon, J.P., Giudice, L.C., Hauser, R., Prins, G.S., Soto, A.M., et al., 2009. Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr. Rev. 30, 293–343.

Ejaredar, M., Nyanza, E.C., Ten Eycke, K., Dewey, D., 2015. Phthalate exposure and childrens neurodevelopment: a systematic review. Environ. Res. 142 (June), 51–60. doi:http://dx.doi.org/10.1016/j.envres.2015.06.014.

Evans, S.F., Kobrosly, R.W., Barrett, E.S., Thurston, S.W., Calafat, A.M., Weiss, B., Stahlhut, R., Yolton, K., Swan, S.H., 2014. Prenatal bisphenol A exposure and maternally reported behavior in boys and girls. Neurotoxicology 45 (December), 91–99. doi:http://dx.doi.org/10.1016/j.neuro.2014.10.003 (Epub 2014 Oct 13).

Fisher, M., Arbuckle, T.E., Mallick, R., LeBlanc, A., Hauser, R., Feeley, M., Koniecki, D., Ramsay, T., Provencher, G., Bérubé, R., Walker, M., 2015. Bisphenol A and phthalate metabolite urinary concentrations: daily and across pregnancy variability. J Expo. Sci. Environ. Epidemiol. 25 (May (3)), 231–239. doi:http://dx.doi.org/10.1038/jes.2014.65 (Epub 2014 Sep 24).

Froehlich, T.E., Lanphear, B.P., Auinger, P., Hornung, R., Epstein, J.N., Braun, J., Kahn, R. S., 2009. Association of tobacco and lead exposures with attention-deficit/hyperactivity disorder. Pediatrics 124, e1054–e1063.
Golub, M.S., Wu, K.L., Kaufman, F.L., Li, L.-H., Moran-Messen, F., Zeise, L., Alexeff, G.V., Donald, J.M., Bisphenol, A., 2010. developmental toxicity from early prenatal exposure. Birth Defects Res. 89 (Pt. B), 441–466.
Goodlad, J.K., Marcus, D.K., Fulton, J.J., 2013. Lead and Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms: a meta-analysis. Clin. Psychol. Rev. 33 (April (3)), 417–425.
Goodman, R., Scott, S., 1999. Comparing the strengths and difficulties questionnaire and the child behavior checklist: is small beautiful? J. Abnorm. Child Psychol. 27 (February (1)), 17–24.
Grandjean, P., Landrigan, P.J., 2014. Neurobehavioural effects of developmental toxicity. Lancet Neurol. 13 (March (3)), 330–338.
Hajszan, T., Leranth, C., 2010. Bisphenol A interferes with synaptic remodeling. Front. Neuroendocrinol. 31, 519–530.
Harley, K.G., Gunier, R.B., Kogut, K., Johnson, C., Bradman, A., Calafat, A.M., Eskenazi, B., 2013. Prenatal and early childhood bisphenol A concentrations and behavior in school-aged children. Environ. Res. 126 (October), 43–50.
Health Canada, Environment Canada, 2000. Priority Substances List Assessment Report for Butylbenzylphthalate. . (accessed 20.05.15) ISBN: 0-662-28192-6. Cat. No.: En 40-215/44E. (Archived June 24, 2013) http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/psl2-lsp2/butylbenzylphthalate/index-eng.php#a2.2.1.
Health Canada, 2010. Report on Human Biomonitoring of Environmental Chemicals in Canada, Results of the Canadian Health Measures Survey Cycle 1 (2007–2009). August. . http://www.hc-sc.gc.ca/ewh-semt/contaminants/human-humaine/index-eng.php.
Heffernan, A.L., Aylward, L.L., Samidurai, A.J., Davies, P.S., Toms, L.M., Sly, P.D., Mueller, J.F., 2014. Short term variability in urinary bisphenol A in Australian children. Environ. Int. 68 (July), 139–143.
Helsel, D.R., 2012. Statistics for Censored Environmental Data Using Minitab and R, 2nd. ed. John Wiley & Sons, Hoboken.
Hong, S.B., Hong, Y.C., Kim, J.W., Park, E.J., Shin, M.S., Kim, B.N., Yoo, H.J., Cho, I.H., Bhang, S.Y., Cho, S.C., 2013. Bisphenol A in relation to behavior and learning of school-age children. J. Child Psychol. Psychiatry 54 (August (8)), 890–899.
Hong, S.B., Im, M.H., Kim, J.W., Park, E.J., Shin, M.S., Kim, B.N., Yoo, H.J., Cho, I.H., Bhang, S.Y., Hong, Y.C., Cho, S.C., 2015. Environmental lead exposure and attention-Deficit/Hyperactivity disorder symptom domains in a community sample of south korean school-Age children. Environ. Health Perspect. 123 (March (3)), 271–276. doi:http://dx.doi.org/10.1289/ehp.1307420.
Huang, P.C., Kuo, P.L., Guo, Y.L., Liao, P.C., Lee, C.C., 2007. Associations between urinary phthalate monoesters and thyroid hormones in pregnant women. Hum. Reprod. 22, 2715–2722.
Jurewicz, J., Polańska, K., Hanke, W., 2013. Exposure to widespread environmental toxicants and children's cognitive development and behavioral problems. Int. J. Occup. Med. Environ. Health 26 (April (2)), 185–204.
Kessler, R.C., Foster, C.L., Saunders, W.B., Stang, P.E., 1995. Social consequences of psychiatric disorders, I: educational attainment. Am. J. Psychiatry 152 (July (7)), 1026–1032.
Kim, B.N., Cho, S.C., Kim, Y., Shin, M.S., Yoo, H.J., Kim, J.W., Yang, Y.H., Kim, H.W., Bhang, S.Y., Hong, Y.C., 2009. Phthalates exposure and attention-deficit/hyperactivity disorder in school-age children. Biol. Psychiatry 66 (November (10)), 958–963.
Kobrosly, R.W., Evans, S., Miodovnik, A., Barrett, E.S., Thurston, S.W., Calafat, A.M., Swan, S.H., 2014. Prenatal phthalate exposures and neurobehavioral development scores in boys and girls at 6–10 years of age. Environ. Health Perspect. 122 (May (5)), 521–528. doi:http://dx.doi.org/10.1289/ehp.1307063 (Epub 2014 Feb 21).
Krueger, R.F., McGue, M., Iacono, W.G., 2001. The higher-order structure of common DSM mental disorders: internalization, externalization, and their connections to personality. Pers. Individ. Diff. 30, 1245–1259.
Lavigne, J.V., Hopkins, J., Gouze, K.R., Bryant, F.B., LeBailly, S.A., Binns, H.J., Lavigne, P. M., 2011. Is smoking during pregnancy a risk factor for psychopathology in young children? A methodological caveat and report on preschoolers. J. Pediatr. Psychol. 36 (January (1)), 10–24.
Levy, S., Katusic, S.K., Colligan, R.C., Weaver, A.L., Killian, J.M., Voigt, R.G., Barbaresi, W.J., 2014. Childhood ADHD and risk for substance dependence in adulthood: a longitudinal, population-based study. PLoS One 9 (August (8)), e105640. doi:http://dx.doi.org/10.1371/journal.pone.0105640 (eCollection 2014).
Lohr, S., 2010. Sampling: Design and Analysis, 2nd ed. Brooks/Cole Cengage Learning, Boston.
McCrory, C., Layte, R., 2012. Prenatal exposure to maternal smoking and childhood behavioural problems: a quasi-experimental approach. J. Abnorm. Child Psychol. 40 (November (8)), 1277–1288.
Meeker, J.D., Ferguson, K.K., 2011. Relationship between urinary phthalate and bisphenol A concentrations and serum thyroid measures in U.S. adults and adolescents from the National Health and Nutrition Examination Survey (NHANES) 2007–2008. Environ. Health Perspect. 119 (October (10)), 1396–1402. doi:http://dx.doi.org/10.1289/ehp.1103582 (Eub 2011 Jul 11).
Morales, E., Julvez, J., Torrent, M., Ballester, F., Rodríguez-Bernal, C.L., Andiarena, A., Vegas, O., Castilla, A.M., Rodriguez-Dehli, C., Tardón, A., Sunyer, J., 2015. Vitamin D in pregnancy and attention deficit hyperactivity disorder-like symptoms in childhood. Epidemiology 26 (July (4)), 458–465. doi:http://dx.doi.org/10.1097/EDE.0000000000000292.
Mustieles, V., Pérez-Lobato, R., Olea, N., Fernández, M.F., 2015. Bisphenol A: human exposure and neurobehavior. Neurotoxicology 49 (July), 174–184. doi:http://dx.doi.org/10.1016/j.neuro.2015.06.002 (Epub 2015 Jun 27).
Narita, M., Miyagawa, K., Mizuo, K., Yoshida, T., Suzuki, T., 2006. Prenatal and neonatal exposure to low-dose of bisphenol-A enhance the morphine-induced hyperlocomotion and rewarding effect. Neurosci. Lett. 402 (July (3)), 249–252 (Epub 2006 May 6).
Neufang, S., Specht, K., Hausmann, M., Gunturkun, O., Herpetz-Dahlmann, B., Fink, G.R., Konrad, K., 2009. Sex differences and the impact of steroid hormones on the developing human brain. Cereb. Cortex 19, 464–473.
Owens, J., Gruber, R., Brown, T., Corkum, P., Cortese, S., O'Brien, L., Stein, M., Weiss, M., 2013. Future research directions in sleep and ADHD: report of a consensus working group. J. Atten. Disord. 17 (October (7)), 550–564. doi:http://dx.doi.org/10.1177/1087054712457992 (Epub 2012 Sep 13).
Park, S., Lee, J.M., Kim, J.W., Cheong, J.H., Yun, H.J., Hong, Y.C., Kim, Y., Han, D.H., Yoo, H.J., Shin, M.S., Cho, S.C., Kim, B.N., 2015. Association between phthalates and externalizing behaviors and cortical thickness in children with attention deficit hyperactivity disorder. Psychol. Med. 45 (June (8)), 1601–1612. doi:http://dx.doi.org/10.1017/s0033291714002694.
Perera, F., Vishnevetsky, J., Herbstman, J.B., Calafat, A.M., Xiong, W., Rauh, V., Wang, S., 2012. Prenatal bisphenol A exposure and child behaviour in an inner city cohort. Environ. Health Perspect. 120 (August (8)), 1190–1194.
Quinn, P.O., 2008. Attention-deficit/hyperactivity disorder and its comorbidities in women and girls: an evolving picture. Curr. Psychiatr. Rep. 10, 419–423.
Refetoff, S., Weiss, R.E., Usala, S.J., Hayashi, Y., 1994. The syndromes of resistance to thyroid hormones: update 1994. In: Braverman, L.E., Refetoff, S. (Eds.), Clinical and Molecular Aspects of Diseases of the Thyroid, vol. 3. Endocrine Society, Bethesda, MD, pp. 336–343.
Rochester, J.R., 2013. Bisphenol A and human health: a review of the literature. Reprod. Toxicol. 42 (December), 132–155.
Roen, E.L., Wang, Y., Calafat, A.M., Wang, S., Margolis, A., Herbstman, J., Hoepner, L.A., Rauh, V., Perera, F.P., 2015. Bisphenol A exposure and behavioral problems among inner city children at 7–9 years of age. Environ. Res. 142 (October), 739–745. doi:http://dx.doi.org/10.1016/j.envres.2015.01.014.
Roza, S.J., Verhulst, F.C., Jaddoe, V.W., Steegers, E.A., Mackenbach, J.P., Hofman, A., Tiemeier, H., 2009. Maternal smoking during pregnancy and child behaviour problems: the Generation R Study. Int. J. Epidemiol. 38 (June (3)), 680–689.
Statistics Canada, 2008. The Participation and Activity Limitation Survey. . (accessed 06.10.14) http://www.statcan.gc.ca/pub/89-628-x/2007002/4125020-eng.htm#a4.
Statistics Canada, 2011. Canadian Health Measures Survey (CHMS): Data User Guide Cycle 1. . (accessed 20.05.15) http://www23.statcan.gc.ca/imdb-bmdi/document/5071_D2_T1_V1-eng.htm.
Suzuki, T., Mizuo, K., Nakazawa, H., Funae, Y., Fushiki, S., Fukushima, S., Shirai, T., Narita, M., 2003. Prenatal and neonatal exposure to bisphenol-A enhances the central dopamine D1 receptor-mediated action in mice: enhancement of the methamphetamine-induced abuse state. Neuroscience 117 (3), 639–644.
Teitelbaum, S.L., Britton, J.A., Calafat, A.M., Ye, X., Silva, M.J., Reidy, J.A., Galvez, M.P., Brenner, B.L., Wolff, M.S., 2008. Temporal variability in urinary concentrations of phthalate metabolites, phytoestrogens and phenols among minority children in the United States. Environ. Res. 106 (February (2)), 257–269.
Testa, C., Nuti, F., Hayek, J., De Felice, C., Chelli, M., Rovero, P., Latini, G., Papini, A.M., 2012. Di-(2-ethylhexyl) phthalate and autism spectrum disorders. ASN Neuro 4 (May (4)), 223–229. doi:http://dx.doi.org/10.1042/AN20120015.
Togashi, M., Nguyen, P., Fletterick, R., Baxter, J.D., Webb, P., 2005. Rearrangements in thyroid hormone receptor charge clusters that stabilize bound 3,5′,5-triiodo–thyronine and inhibit homodimer formation. J. Biol. Chem. 280 (July (27)), 25665–25673.
U.S. Consumer Product Safety Commission, 2014. Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives. July. . (accessed 09.10.14) http://www.cpsc.gov/PageFiles/169902/CHAP-REPORT-With-Appendices.pdf.
Watkins, D.J., Eliot, M., Sathyanarayana, S., Calafat, A.M., Yolton, K., Lanphear, B.P., Braun, J.M., 2014. Variability and predictors of urinary concentrations of phthalate metabolites during early childhood. Environ. Sci. Technol. 48 (August (15)), 8881–8890.
Weiss, B., 2012. The intersection of neurotoxicology and endocrine disruption. Neurotoxicology 33 (December (6)), 1410–1419.
Whyatt, R.M., Liu, X., Rauh, V.A., Calafat, A.M., Just, A.C., Hoepner, L., Diaz, D., Quinn, J., Adibi, J., Perera, F.P., Factor-Litvak, P., 2012. Maternal prenatal urinary phthalate metabolite concentrations and child mental, physchomotor and behavioral development at age three years. Environ. Health Perspect. 120 (February (2)), 290–295.
Winneke, G., 2011. Developmental aspects of environmental neurotoxicology: lessons from lead and polychlorinated biphenyls. J. Neurol. Sci. 308 (1–2), 9–15. doi:http://dx.doi.org/10.1016/j.jns.2011.05.020 (Epub 2011 Jun 15).
Wolstenholme, J.T., Rissman, E.F., Connelly, J.J., 2011. The role of bisphenol A in shaping the brain, genome and behaviour. Horm. Behav. 59, 296–305.
Zoeller, R.T., 2006. Collision of basic and applied approaches to risk assessment of thyroid toxicants. Ann. N. Y. Acad. Sci. 1076 (Septemeber), 168–190.