Neurobehavioral Deficits, Diseases and Associated Costs of Exposure to Endocrine Disrupting Chemicals in the European Union

Martine Bellanger,[1]
Barbara Demeneix,[2], Philippe Grandjean,[3,4], R. Thomas Zoeller,[5]
Leonardo Trasande[6,7,8,9,]

[1]EHESP School of Public Health, Paris, France; [2]UMR 7221 CNRS/MNHN, Muséum National d'Histoire Naturelle, Paris, France; [3]Harvard School of Public Health, Boston, MA, USA; [4]University of Southern Denmark, Odense, Denmark; [5]University of Massachusetts, Amherst, MA, USA; [6]New York University (NYU) School of Medicine, NY, New York, USA; [7]NYU Wagner School of Public Service, NY, New York, USA; [8]NYU Steinhardt School of Culture, Education and Human Development, Department of Nutrition, Food & Public Health, NY, New York, USA; [9]NYU Global Institute of Public Health, NY University, NY, New York, USA

Context: Epidemiological studies and animal models demonstrate that endocrine disrupting chemicals (EDCs) contribute to cognitive deficits and neurodevelopmental disabilities.

Objective: To estimate neurodevelopmental disability and associated costs that can be reasonably attributed to EDC exposure in the European Union.

Design: An expert panel applied a weight-of-evidence characterization adapted from the Intergovernmental Panel on Climate Change. Exposure-response relationships and reference levels were evaluated for relevant EDCs, and biomarker data were organized from peer-reviewed studies to represent European exposure and approximate burden of disease. Cost estimation as of 2010 utilized lifetime economic productivity estimates, lifetime cost estimates for autism spectrum disorder (ASD) and annual costs for attention deficit hyperactivity disorder (ADHD).

Setting, Patients and Participants and Intervention: Cost estimation was carried out from a societal perspective, i.e. including direct costs (e.g. treatment costs) and indirect costs such as productivity loss.

Results: The panel identified 70–100% probability that polybrominated diphenyl ether (PBDE) and organophosphate (OP) exposures contribute to IQ loss in the European population. PBDE exposures were associated with 873,000 (sensitivity analysis: 148,000–2.02 million) lost IQ points and 3,290 (sensitivity analysis: 3,290–8,080) cases of intellectual disability, at costs of €9.59 billion (sensitivity analysis: €1.58–22.4 billion). OP exposures were associated with 13.0 billion (sensitivity analysis: 4.24–17.1 billion) lost IQ points and 59,300 (sensitivity analysis: 16,500–84,400) cases of intellectual disability, at costs of €146 billion (sensitivity analysis: €46.8–194 billion). ASD causation by multiple EDCs was assigned a 20–39% probability, with 316 (sensitivity analysis: 126–631) attributable cases at a cost of €199 million (sensitivity analysis: €79.7–399 million). ADHD causation by multiple EDCs was assigned a 20–69% probability, with 19,300–31,200 attributable cases at a cost of €1.21–2.86 billion.

Conclusions: EDC exposures in Europe contribute substantially to neurobehavioral deficits and disease, with a high probability of >€150 billion costs/year. These results emphasize the advantages of controlling EDC exposure.

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received December 8, 2014. Accepted March 1, 2015.

Abbreviations: Acetylcholinesterase (AChE); Attention Deficit and Hyperactivity Disorder (ADHD); Attributable Fraction (AF); Autism Spectrum Disorder (ASD); Childhood and Adolescent Disorders (CAD); Exposure-Response Relationship (ERR); Gross Domestic Product (GDP); Intellectual Quotient (IQ); Odds Ratio (OR); Polybrominated Diphenyl Ether (PBDE); Purchasing Power Parity (PPP);

The central nervous system (CNS) is uniquely sensitive to adverse effects of chemical exposures during early (especially fetal, though through pubertal) development (1, 2), and endocrine disruption has emerged as an important mechanism by which chemicals may have adverse effects on the developing brain, whether by interfering with thyroid hormone or sex steroid actions, or via other hormonal modes of action (3).

Thyroid hormone is particularly important for normal brain development, and both clinical and animal research provides confidence in the assertion that thyroid disruption will affect brain development (4–7). Predictable outcomes of thyroid disruption include global IQ deficits and neurodevelopment disabilities such as autism spectrum disorder (ASD), and attention-deficit hyperactivity disorder (ADHD) (7–12). Classes of chemicals such as polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) and organophosphate pesticides (OP) have been shown to interfere with thyroid hormone action in humans and in laboratory studies (13). The human population is ubiquitously exposed to these chemicals (14), and several high-quality studies have documented adverse outcomes. Moreover, ASD and ADHD are common disorders with global prevalence rates in 2010 of 6.2–7.6/1,000 (15, 16) and 6.1% (17), respectively. Both outcomes are complex and heterogeneous with both genetic and environmental origins.

Environmental exposures, including lead, methylmercury, arsenic, certain drugs, tobacco smoke and pesticides, have been linked to ASD as well as ADHD (18–24). While these conditions may be identified in individual children, developmental neurotoxicity may also affect brain function in more subtle and insidious ways, resulting in cognitive deficits that affect much larger numbers of undiagnosed children, sometimes referred to as a "chemical brain drain" (1).

Resulting neurodevelopmental disabilities are costly to the affected individuals, their families and to society. For example in 2010, the lifetime societal cost per individual with ASD without intellectual disability was estimated to be about $1.4 million in the US and the UK, driven chiefly by adult productivity loss (25). Likewise, national annual costs for ADHD in the Netherlands were found to be between €1.04–1.53 billion, including lost parental productivity and income (26). In the EU costs for environmentally attributable childhood and adolescent disorders (CADs, defined to include ASD, ADHD and conduct disorder) and intellectual disability were previously estimated to be nearly $10 billion (27), though these estimates preceded very recent studies documenting IQ loss in association with exposures to PBDEs and OPs (28–30).

In the context of emerging evidence regarding EDC contribution to neurodevelopmental disease and disability, and well developed methods for calculating economic impacts of cognitive deficits and neurobehavioral disorders (31), the present report attempts to utilize current epidemiological and mechanistic data linking EDC exposure to neurobehavioral outcomes to estimate the attributable disease burden and costs to society. As environmental contributions to the burden of disease may be easily underestimated due to uncertainties in the evidence (32), our goal was to generate realistic estimates based on the strength of evidence using a framework first developed in regard to climate change (33, 34). We focused on costs attributable to exposures in Europe in the context of active regulatory decision-making on EDCs.

Materials and Methods

Overall approach

Based on the above evidence, the expert panel focused on four exposure-outcome relationships with the greatest evidence for causation: PBDE exposure with reduced cognition, OP exposure with reduced cognition, endocrine disruptor exposures (including phthalates) with ASD, and endocrine disruptor exposures (including OP and PBDE) and attention deficit hyperactivity disorder (ADHD). The panel selected these exposure-outcome relationships because of the presence of well-conducted longitudinal human and animal studies to assess developmental neurotoxic effects of these EDCs. We adhered to the approach described in the accompanying overarching manuscript (35) in evaluating strength of the epidemiologic (using the WHO GRADE Working Group criteria) (36, 37) and toxicologic literature (using the Danish Environmental Protection Agency criteria) (38), and to assigning probability of causation (adapting the Intergovernmental Panel on Climate Change criteria) (33). An appendix describes exposure biomarker inputs used to model exposure in the EU and approaches to valuing costs of reduced cognition, ASD and ADHD, while subsequent sections describe estimation of affected populations and attributable prevalence/incidence.

Modeling PBDE-47 and Organophosphate Associated IQ loss and Intellectual Disability

The numbers of births in the year 2010 in the EU were calculated to represent the percentile ranges 0-ninth, 10–24th, 25–49th, 50–74th, 75–89th, and 90–99th to allow application of estimates of exposure across each range. The lowest grouping was assumed to have no exposure, while the other groups were assumed to have levels corresponding to the lowest extreme (eg, 10th percentile for all births in the 10–24th percentile grouping). The panel selected the exposure-response relationship (ERR) from longitudinal birth cohort study with the prenatal PBDE levels most closely corresponding to levels found within the EU (39) and applied a reference level corresponding to the 10th percentile in the longitudinal study to model IQ loss in each of the five higher exposure groups. Births for each country in 2010 were obtained from Eurostat (40). The exposure-associated IQ point loss was multiplied by the number of births in each percentile

range to calculate the total IQ loss within each exposure interval. The sum of these losses produced best estimate of the IQ loss due to prenatal PBDE exposures. The expert panel also applied an alternate higher exposure-response relationship from one of the other two longitudinal cohort studies associating IQ loss with prenatal exposure (29) as input to a sensitivity analysis, thus recognizing the uncertainty in the exposure-response relationship that remains despite substantial research.

We also modeled increases in intellectual disability, defined as IQ < 70, assuming a normal distribution with mean 100 and SD 15. Within each exposed group, the NORMDIST function in Microsoft Excel 2010 (Redmond, WA, USA) was used to identify increases in intellectual disability associated with the associated decrement in IQ. The increase in percent with intellectual disability across percentiles of exposure was multiplied by each country's population estimate to quantify attributable cases of intellectual disability to PBDE exposure, and these estimates were aggregated to quantify the total EU burden.

We followed a nearly identical approach with OPs, in which the population of births was divided into identical percentile ranges. The ERR represented a sample size-weighted average of results from two longitudinal birth cohorts, (28, 41) with results from each cohort used as inputs for extrapolation in sensitivity analyses. After applying the ERR described by Bellinger, (42) estimates of total IQ points lost utilized the above-mentioned birth data from Eurostat (40).

Estimating EDC-Attributable Autism

The expert panel chose a longitudinal study of prenatal phthalate exposure from which to extrapolate ranges for potential burden of autism attributable to EDC exposures (43). This study was selected because of its unique measurement of autistic behavior, confounders and biomarkers of EDC exposure in a prospective longitudinal design. No similar studies on this issue were identified. As with OP and PBDE-attributable IQ loss, the population was divided into percentile ranges with levels assigned to groups at the lowest extreme of the percentile range.

Increments in social responsiveness score (SRS), a quantitative scale for measuring the severity of social impairment related to ASD in the general population, were calculated by multiplying the log(base exp) of the ratio of the maternal urinary low molecular weight (LMW) phthalate in each percentile to the presumed reference level (the maternal urinary LMW phthalate estimated for the 10–24th percentile exposure group) by the increment per log unit increase identified by Miodovnik et al (1.53) (43). We also modeled shifts in the distribution of SRS, assuming a normal distribution of mean of 29.7 and an SD of 16.8, as identified from normative data, (44) using the NORMDIST function. Severe social impairment is typically identified as SRS ≥ 75. Incremental increases in autism attributable to phthalates were determined by subtracting the percentage of SRS ≥ 75 in each exposed group minus the percentage of SRS ≥ 75 in the unexposed scenario. These increments were aggregated and divided by 0.62%, the more conservative of the two recent global autism prevalence because of its exclusion of Asperger's syndrome, (15) to quantify one data input for the ASD attributable fraction (AF). The expert panel then considered a range of AF including a base case estimate, accounting for other EDCs plausibly associated with ASD but for which no similar studies were available. These AFs were multiplied by the number of 8-year olds with autism, which was estimated by multiplying the 0.62% prevalence by each country's population estimate of 8-year olds in 2010 obtained from Eurostat (45). These estimates assume that prevalence is equivalent to cumulative incidence of ASD, positing that early life EDC exposures manifest at various time points before age 8.

Estimating EDC-Attributable ADHD

In attributing ADHD to EDC exposures, the expert panel identified positive longitudinal studies for OP pesticide and PBDE exposure in pregnancy (22, 23). To avoid double counting, the expert panel chose to extrapolate a range of attributable burdens of disease using studies of these two exposures, rather than assuming additive effects of these two exposures in their contribution to ADHD. As a conservative measure the panel chose to use a cross-sectional study of OP exposure (19) that identified a more modest exposure-response relationship than the longitudinal study (22). Following the approach described for ASD, odds ratios in the Bouchard et al study (19)were exponentiated by the log(base 10) unit of the ratio of the total dialkyl phosphate concentration in each EU exposure group by 65.0 nmol/L, the reference level used to calculate IQ loss. Recognizing that ADHD is more prevalent than ASD, and that use of an odds ratio (OR) rather than a relative risk in the Levin equation (46) could produce overestimation of the AF, adjustment was applied to estimate the relative risk (47). The OR for each group was input along with the percentage of the population with that range of exposure into the Levin equation to calculate AFs (46). The AFs were then summed across the exposed groups to identify an aggregate OP AF for ADHD. The Gascon study identified an OR of 1.80 for ADHD among the 20% with detectable levels compared to others with nondetectable levels. After correction to RR as above, these values were used to generate an AF for PBDEs.

The expert panel used the OP AF as a base case estimate, and the PBDE AF as a sensitivity analytic input. Following the same approach made for ASD, the estimated AFs for ADHD were multiplied by the 6.1% global prevalence of ADHD (17). As with ASD, we utilized prevalence as a proxy for cumulative incidence.

Results

PBDE-Attributable IQ Loss and Intellectual Disability

The expert panel identified moderate-to-high epidemiologic evidence for IQ loss attributable to PBDE exposure. The panel identified four well-designed longitudinal observational studies (birth cohorts). Three of the studies (48–50) identified consistent, exposure-response relationships with IQ, with carefully collected data on many potential confounders. The fourth study, from Spain, suffered from modest sample size, with few detectable PBDE levels, though this study showed substantial directionality towards cognitive and motor dysfunction at age 4; (23) IQ was not measured. It should be noted that the three other studies were of US populations. This is relevant because exposure levels in the US are much higher than in the EU. The congener distribution is different in the EU, with sub-

stantially higher levels of PBDE-47, the congener most consistently associated with cognitive deficits, than in the US.

Exposure-response relationships for PBDE-47 from these longitudinal birth cohorts were selected to develop a range of exposure-response relationships, with a reference level of 2.82 ng/g, corresponding to the 10th percentile in the longitudinal cohort study (39) which the panel selected for extrapolation in the base case scenario. The Menorca, Spain cohort had a median cord blood concentration of 2.1 ng/g; it found positive directionality, though did not reach statistical significance ($P > .05$), suggesting that the selection of a reference level of 2.82 ng/g is conservative. This reference level is also supported by data from animals, which document interference with thyroid function by PBDE-47 in fetal lambs at exposures of 0.2 μg/kg birth weight per day (51), ie, serum concentrations only slightly above those that are prevalent in the EU (52–54). Additional support comes from the US Environmental Protection Agency use of a benchmark dose approach to develop a reference dose of 0.1 μg/kg b.w. per day based on neurotoxicity in mice (55, 56). Further, the European Food Safety Authority calculated that current exposures are less than one-tenth of the benchmark dose for various population groups at risk, thus leaving a fairly small margin of exposure (57).

The panel concluded that there is strong evidence for an endocrine mode of action of PBDEs contributing to IQ loss. The foundation of this conclusion is the evidence that PBDE exposure interferes with thyroid hormone action during development, and that interference with thyroid hormone action causes IQ loss. Appendix Table 1 tabulates the evidence, from humans, animals and in vitro, that PBDE interferes with thyroid hormone action. In addition to modulating interaction of thyroid hormone with its receptor, these substances may also affect the metabolism of thyroid hormone (58). Thyroid hormone is essential for normal brain development (5), and thyroid hormone insufficiency during development can produce different effects on the brain depending on the timing of the insult (6, 59), and such deficits persist into adulthood (60). However, PBDE-associated developmental neurotoxicity may occur without detectable changes in thyroid function (61). Also, several potential non-EDC mechanisms have been highlighted (62), but the preponderance of the literature suggests that thyroid disruption plays an important role in the pathogenesis of PBDE-induced developmental neurotoxicity.

IQ loss was estimated to occur only in the highest two percentile fractions of the EU population in base case analyses (0.52 to 0.84 IQ points), with alternative scenarios ranging from IQ loss only in the highest quantile (0.27 points) to larger IQ losses in the two higher quantiles (1.19 to 1.94 points). In total, 873 000 IQ points were estimated to be lost annually (sensitivity analyses: 149 000–2.02 million), with associated productivity loss of €8.40 billion (sensitivity analyses: €1.43 to 19.4 billion). An additional 3290 (sensitivity analyses: 544–8080) cases of intellectual disability were estimated, with €1.19 billion (sensitivity analyses: €148 million to €2.93 billion in associated social costs.

Together the evaluation of the epidemiologic and toxicologic evidence led to the assessment of a 70%–100% probability that PBDE neurotoxicity costs the EU €9.59 billion (sensitivity analyses: €1.58 to €22.4 billion) annually, using the IPCC criteria (Table 1).

Table 1. PBDE-Associated IQ Loss, Intellectual Disability and Costs, European Children Born in 2010

Expert Panel Evaluation of Epidemiologic Evidence	**Moderate-to-high**					
Expert Panel Evaluation of Toxicologic Evidence	Strong					
Probability of Causation	70–100%					
Percentile of Exposure	0–9	10–24	25–49	50–74	75–89	>90
Percentile Assumed	0	10	25	50	75	90
Cord Blood PBDE, ng/g (Base Case)	0.00	0.00	0.00	2.60	4.61	6.27
Cord Blood PBDE, ng/g (Sensitivity Analysis)	0.00	0.00	0.53	1.60	2.68	3.66
IQ loss (Low)	0.00	0.00	0.00	0.00	0.00	0.27
IQ loss (Base Case)	0.00	0.00	0.00	0.00	0.52	0.84
IQ loss (High)	0.00	0.00	0.00	0.00	1.19	1.94
Births	541 000	812 000	1 350 000	1 350 000	812 000	541 000
IQ points lost (Low)	0	0	0	0	0	149 000
IQ points lost (Base Case)	0	0	0	0	418 000	454 000
IQ points lost (High)	0	0	0	0	968 000	1 050 000
Lost Economic Productivity (Low)	1.43 billion					
Lost Economic Productivity (Base Case)	8.40 billion					
Lost Economic Productivity (High)	19.4 billion					
Attributable Intellectual Disability (Low)	544					
Attributable Intellectual Disability (Base Case)	3290					
Atributable Intellectual Disability (Sensitivity Analysis)	8080					
Cost of Intellectual Disability (Low)	148 million					
Cost of Intellectual Disability (Base Case)	1.20 billion					
Cost of Intellectual Disability (High)	2.93 billion					
Total Costs (Low)	1.58 billion					
Total Costs (Base Case)	9.59 billion					
Total Costs (High)	22.4 billion					

Organophosphate (OP) pesticide-Associated IQ Loss, Economic Productivity and Intellectual Disability

The expert panel identified moderate-to-high epidemiologic evidence for IQ loss attributable to OP exposure. The panel identified three well-designed longitudinal observational studies (birth cohorts) (41, 63, 64) which identified consistent, exposure-response relationships with carefully collected data on many potential confounders. These studies were of populations with much lower exposure levels than in the EU, though it should be noted that two of the three studies examined urinary dialkylphosphate (DAP), an indicator of recent (acute exposure approximately a week prior to sampling) exposure to OP pesticides. Though chlorpyrifos is the chief organophosphate pesticide used in Europe, in the US (where these studies were conducted) other pesticides may have contributed to the DAP levels, raising the issue of modest exposure imprecision.

The panel also identified strong toxicological evidence for effect via an endocrine disrupting mechanism. The principal mode of action of chlorpyrifos is through acetyl cholinesterase (AChE) inhibition, though many reports indicate neurotoxicological effects independent of AChE inhibition. Developmental exposure of mice to levels of chlorpyrifos that had no effect on AChE activity in mice adversely affected thyroid hormone levels (65). A number of other animal studies have shown chlorpyrifos to affect thyroid hormone signaling. Jeong et al, (66) carried out a one-generation reproductive toxicity study on chlorpyrifos using doses of 1, 10 and 100 mg/ kg bw/d. They found significant effects on thyroid signaling (either thyroid histology, or circulating levels of T4 and/or TSH) after long-term exposure in utero and through lactation. In terms of neurotoxicity, Levin et al (67) showed that similar exposures (1 or 5 mg/kg birth weight/d) in late gestation (gestational day 17- 20) also produced significant, long-lasting effects on behavior in pups tested in adolescence and adulthood. Interestingly, effects were greater at the lower dose. Furthermore, the four-day period of exposure studied is well known to be both a phase of peak neurogenesis, dependent on maternal thyroid hormone supply (68).

Exposure-response relationships already established were selected to develop a exposure-response relationship in the base case scenario, with a reference level of 65 nmol/L urinary total DAP (42). Bouchard et al (2011) reported that a 10-fold increase in total urinary DAP was associated with a loss of 5.6 IQ points (41, 63), whereas Engel et al (2011) reported that a 10-fold increase was associated with a loss of 1.39 points (69). Weighting the effect estimates by sample size produces an expected loss of 4.25 FSIQ points for a 10-fold increase in urinary DAP over this range.

Detectable OP exposure levels in the EU population, ranging from 79.9–1160.8 nmol/L in base analyses (Table 2), and 34.2–444.8 nmol/L in sensitivity analyses. These levels were associated with decrements in IQ between 0.38–5.32 points in base case scenarios, and a range of 0.12–7.01 lost IQ points in sensitivity analyses. Each year, 13.0 million IQ points are lost (sensitivity analysis: 4.24–17.1 million), with associated productivity loss of €124 billion (sensitivity analysis: €40.8–164 billion). In addition, 59 300 additional cases of intellectual disability were attributed to prenatal organophosphate exposure (sensitivity analysis: 16 500–84 400) across the EU, with an additional €21.4 billion (sensitivity analysis: €5.96–30.5

Table 2. Organophosphate-Associated IQ Loss, Intellectual Disability and Costs, European Children Born in 2010

Expert Panel Evaluation of Epidemiologic Evidence	Moderate-to-high					
Expert Panel Evaluation of Toxicologic Evidence	Strong					
Probability of Causation	70–100%					
Percentile of Exposure	0–9	10–24	25–49	50–74	75–89	>90
Percentile Assumed	0	10	25	50	75	90
Urinary Total Dialkylphosphate, nmol/liter (Base Case)	0.00	79.92	175.55	280.58	741.31	1160.78
Urinary Total Dialkylphosphate, nmol/liter (Sensitivity Analyses)	0.00	34.20	97.30	200.00	370.00	444.79
IQ loss, Base Case Scenario	0.00	0.38	1.83	2.70	4.49	5.32
IQ loss, Low	0.00	0.12	0.60	0.88	1.47	1.74
IQ loss, High	0.00	0.50	2.42	3.56	5.92	7.01
Births	541 000	812 000	1 350 000	1 350 000	812 000	541 000
IQ points lost (Base Case)	0	310 000	2 480 000	3 650 000	3 650 000	2 879 000
IQ points lost (Low)	0	101 000	811 000	1 190 000	1 190 000	942 000
IQ points lost (High)	0	408 000	3 270 000	4 810 000	4 800 000	3 790 000
Lost Economic Productivity (Base Case)	125 billion					
Lost Economic Productivity (Low)	40.8 billion					
Lost Economic Productivity (High)	164 billion					
Attributable Intellectual Disability (Base Case)	59 300					
Attributable Intellectual Disability (Low)	16 500					
Attributable Intellectual Disability (High)	84 400					
Cost of Intellectual Disability (Base Case)	21.4 billion					
Cost of Intellectual Disability (Low)	5.96 billion					
Cost of Intellectual Disability (High)	30.5 billion					
Total Costs (Base Case)	146 billion					
Total Costs (Low)	46.8 billion					
Total Costs (High)	195 billion					

billion) in social costs. The evaluation of the epidemiologic and toxicologic evidence led to an assessment of 70%–100% probability of OP neurotoxicity that costs the EU between €46.8 billion and €195 billion annually.

EDC-Attributable Autism

Due to the paucity of epidemiologic studies, the expert panel identified low epidemiologic evidence for ASD incidence attributable to EDC exposure. The panel identified two informative longitudinal observational studies; (21, 43) while both controlled well for potential confounders, they identified different EDC exposures linked to autism-associated behaviors. Although exposure-response relationships were identified, only a single urinary measure of phthalates in one study raises substantial exposure imprecision concerns which may cause bias towards the null. Phthalates are also a mixture of chemicals with variable androgen and thyroid antagonism. These studies have not followed children to the teenage years, when ASD behaviors would ideally be measured to confirm associations identified in the toddler years. SRS is a nonspecific association, and so this outcome imprecision also reduces confidence in regard to causal attribution.

As a basis for extrapolation to estimate AF of disease for EDCs, the panel used data from a longitudinal birth cohort study identifying increases in prenatal phthalate exposure with increases in SRS, an index used to evaluate autism (43). Using the 10th percentile of exposure in the EU as a reference level, 0.34–1.97 point increases in SRS were identified (Table 3a), with increases in SRS scores over and above the 75 reference level typically associated with autism between 0.021–0.143%. In total, the AF was estimated to be 8.88%, using these assumptions.

The panel was beset with the difficulty that SRS is an intermediate index of autism spectrum features, and that SRS is alone not diagnostic for autism. Therefore, as a conservative measure, the panel chose to use the above estimate as a guide in estimating total EDC AF for autism, rather than attributing the estimated burden of autism directly to phthalates. Recognizing other EDCs besides phthalates as contributors to autism, the panel chose 5% as a base case estimate of AF with 2%–10% as inputs for sensitivity analyses. The panel noted that the Miodovnik increments in SRS (43) were much smaller than those noted in sex-stratified analyses by Braun et al (21). The sex predilection of ASD further suggests the biological plausibility of hormonal mechanisms disrupted by EDCs. The panel also noted twin studies suggesting that approximately 50% of ASD can be attributed to environmental factors (70), though gene-environment interactions can occur through EDC mechanisms. A National Academy of Sciences panel in 2005 identified 28% of neurodevelopmental disabilities including autism to at least be in part due to environmental factors (71).

The panel also noted strong toxicological evidence for autism-associated pathologies via different endocrine disrupting mechanisms. The panel identified moderate evidence for causation for each chemical category. As maternal hypothyroidism increases ASD risk fourfold (72) it is logical to examine links with those EDCs associated with ASD risk in human cohorts with data on thyroid hormone signaling pathways and brain development. This is the case for PBDEs and OPs, as discussed in the previous sections. It is also the case for phthalates, a chemical class for which exposure has been related to increased ASD risk (73). Although most work on the endocrine disrupting effects of phthalates has focused on antiandrogenic effects (74), many epidemiological and animal studies show effects on thyroid hormone signaling. An early rat study (75) reported significant effects of DBP on circulating levels of the active form of thyroid hormone, T_3, and these effects were seen at 250 mg/kg/d, levels half the lowest dose modifying circulating testosterone. The findings in animals associating phthalates with reduced thyroid levels has also been shown in humans through nationally representative cross-sectional studies in the US (76) as well as Danish children aged between 4 and 9 years old (34).

After applying a 0.62% autism prevalence (Table 3b), an estimated 12 300 8-year olds in the EU were autistic, with 316 attributable cases to EDCs (sensitivity analysis: 126–631), after reducing by 48.5% to account for coexisting intellectual disability and avoid double counting. Together the findings suggest a 20%–39% probability that EDC associated ASD costs between €79.8–399 million annually.

EDC-Attributable ADHD

The panel identified three longitudinal and one cross-sectional epidemiologic studies examining EDCs and ADHD, leaving the panel with the consensus of low-to-moderate epidemiologic evidence for ADHD attributable to EDC exposures. The cross-sectional study identified strong exposure-response relationships of dialkylphosphates (DAP), with ADHD diagnosis based upon validated parental questionnaire (19). One longitudinal birth cohort identified a exposure-response relationship of PBDE-47 in child blood at age 4 with attention deficit symptoms (but not with the few cases with ADHD diagnosis), having carefully controlled for many potential confounders (23). The second longitudinal study by Chen et al also found increased hyperactivity scores in children born to mothers with higher PBDE-47 levels than the Gascon et al study, and was also well controlled for confounders (30). The third longitudinal study by Marks et al iden-

Table 3. a. Estimates of Phthalate-Attributable Fractions for Autism, European Children in 2010

Percentile of Exposure	0–9	10–24	25–49	50–74	75–89	>90
Percentile Assumed	0	10	25	50	75	90
Low molecular weight (LMW) phthalates, ng/mL	0.00	21.30	35.40	60.00	212.00	416.00
Increase in Responsiveness Score, assume 10th percentile reference level and 1.53 increase/log(LMW)	0.00	0.00	0.34	0.69	1.53	1.97
Increase in SRS>75, Assuming Mean 30 and SD 13	0.00%	0.00%	0.021%	0.045%	0.106%	0.142%
Attributable Fraction, Assuming Baseline 0.62% Prevalence	0.00%	0.00%	1.45%	3.03%	7.21%	9.68%
Overall Attributable Fraction	8.88%					

3b. Estimates of Endocrine Disruptor Attributable Autism and Costs, European Children in 2010

Expert Panel Evaluation of Epidemiologic Evidence	Low
Expert Panel Evaluation of Toxicologic Evidence	Moderate
Probability of Causation	20–39%
Attributable Fraction (Sensitivity Analysis)	5% (2–10%)
Prevalence of Autism	0.62%
Autism Cases, 8-Year Olds	12 300
Attributable Autism Cases after Accounting for Coexistent Intellectual Disability, 2010 (Sensitivity Analysis)	316 (126–631)
Attributable Lifetime Autism Costs, 2010 (Sensitivity Analysis)	199 million (79.7-399 million)

tified increased frequency of symptom-based ADHD diagnosis, though not with visual attention, in a exposure-response relationship to maternal urinary dialkylphosphate levels. The Gascon et al study controlled for PCB, DDE, DDT and HCB (but not OP) exposures (23), while the Chen et al studies was unable to control for other EDC exposures (30). Only the Gascon et al studies are of European origin, though exposures in the other two US-based studies are of much lower exposures, and EU exposures to alkylphosphates are thought to be mainly chlorpyrifos. Exposure-response gradients were defined in the Chen et al (30) and Marks et al (22) studies, but not in the Gascon et al study which included very few cases (23). Although the substances involved are EDCs, the studies did not consider EDC-related pathogenesis.

The panel concluded that there is strong evidence for the ability of endocrine disruption to contribute to ADHD incidence in humans. Humans with generalized resistance to thyroid hormone have a high risk of ADHD (77) and this is related to a genetic mutation in TRβ (78). A reproduction of this mutation in mice also leads to ADHD-like behaviors (79). Moreover, low serum thyroid hormone in

pregnant women are linked to ADHD (80) and low thyroid hormone in pregnant rodents also leads to ADHD-like behaviors in the offspring (81). Although animal models for ADHD are difficult to establish, chemicals that interfere with thyroid hormone action (including PCBs and BPA) also produce ADHD-like activity in rodent studies (82, 83). Corroborating evidence from pregnancy cohorts in humans demonstrate that maternal subclinical and clinical hypothyroidism both contribute to ADHD (21, 56, 70). As PBDE and OPs have been previously described as thyroid inhibitors, the mechanistic link for an EDC-mediated effect on ADHD risk is strong.

As a basis for extrapolation to estimate AFs for EDCs, the panel decided to calculate two AFs, using the Bouchard et al (19) and Gascon et al (23) study, respectively. The panel decided against use of the Marks et al study (22), which showed stronger ADHD associations, while association with attention tests could not be demonstrated. Using data from a cross-sectional study of urinary dialkylphosphates (19) to extrapolate potential EDC-attributable burden, effects were identified in the most highly exposed half of the population with estimated relative risk of ADHD between 1.03–1.42 (Table 4a). AFs of 10.8–17.3% were identified, with 19 400–31 200 children with ADHD after excluding 44.3% of potentially attributable cases due to coexistent intellectual disability. The costs of these cases were estimated to be €2.40 billion (sensitivity analyses: €1.21–2.86 billion). Using data from Gascon et al (23), a higher AF of 12.5% was applied, resulting in an estimated €1.74 billion (Table 4b; sensitivity analyses: €1.41–2.07 billion). Together, these analyses suggest a 20%–69% probability that EDC-associated ADHD costs the EU between €1.21–2.86 billion.

Discussion

Economic calculations have been used to help prioritize societal investments in health care, environmental protection, and other important sectors (84). Adverse effects of neurodevelopmental toxicity have recently emerged as an important public policy concern (1, 2). For example, the global costs due to pollutants, such as lead (27, 85) and methylmercury (31, 86) are very substantial, and this evidence has helped inspire global efforts to phase out the use of leaded fuel and control the releases of mercury and other air pollutants to the environment (87, 88).

The present study builds upon this experience and extends the calculations of societal expenses due to neurodevelopmental toxicity associated with exposure to endocrine disruptors. The calculations on costs due to cognitive deficits show that the few substances that were suitable to analyze are associated with costs that total over €150 billion per year within the EU. This is a likely an underestimate due to the exclusion of neurotoxicant effects of EDCs banned by Europe (eg, under the Stockholm Convention), such as polychlorinated biphenyls. The main cost is due to widespread occurrence of cognitive deficits expressed in terms of IQ points lost, while a sizeable, though smaller, amount is associated with specific diagnoses of ASD and

Table 4. a. Extrapolating EDC-Attributable ADHD and Costs for Organophosphate, European Children in 2010

Percentile of Exposure	0–9	10–24	25–49	50–74	75–89	>90
Percentile Assumed	0	10	25	50	75	90
Total urinary alkyl phosphate, nmol/liter (Base Case)	0.00	79.92	175.55	280.58	741.31	1160.78
Total urinary alkyl phosphate, nmol/liter (Sensitivity Analyses)	0.00	34.20	97.30	200.00	370.00	444.79
Estimated relative risk, ADHD (Base Case)	1.00	1.03	1.13	1.19	1.34	1.42
Estimated relative risk, ADHD (Sensitivity Analyses)	1.00	1.00	1.05	1.15	1.24	1.26
Attributable Fraction (Base Case)	17.28%					
Attributable Fraction (Sensitivity Analyses)	10.76%					
Prevalence among 12 yr olds, ADHD	6.10%					
Attributable ADHD Cases after Accounting for Coexistent Intellectual Disability, 2010 (Base Case)	31 154					
Attributable ADHD Cases after Accounting for Coexistent Intellectual Disability, 2010 (Sensitivity Analyses)	19 388					
Cost of Attributable Cases (Sensitivity Analysis)	2.40 billion (1.21–2.86 billion)					

4b. Extrapolating EDC-Attributable ADHD and Costs for PBDE, European Children in 2010

Percent Exposed	20%
Odds ratio, ADHD	1.80
Attributable Fraction	12.53%
Prevalence among 12 yr olds, ADHD	6.10%
Attributable ADHD Cases after Accounting for Coexistent Intellectual Disability, 2010	22 600
Cost of Attributable Cases (Sensitivity Analysis)	1.74 billion (1.41–2.07 billion)

ADHD. This finding is in accordance with results obtained for, eg, mercury, where costs associated with cognitive deficits are much greater than those associated with specific diagnoses (89).

We endeavored to make our estimates as precise as possible, but were limited due to sizable uncertainties in the evidence. Thus, although these calculations were based on a small number of chemicals for which we have data, they illustrate for the first time that neurotoxicity associated with endocrine disruption is very costly to society. Insofar as other PBDEs have effects beyond those of PBDE-47, our estimates may be substantially conservative. These calculations do not include the costs due to potential cognitive deficits associated with exposures to, eg, phthalates (90) or perchlorate, a thyroid hormone disruptor (91). We also did not examine the potential for synergistic effects between EDCs which might heighten the effects of a single EDC exposure. Given that SRS is an intermediate index of autism spectrum features, and that SRS is not a diagnostic test for autism, the panel chose to err on the conservative side, and use a lower base estimate for attributing autism, and using this estimate for autism attributable to all EDCs. We were also limited by a paucity in European data on exposure-outcome relationships; while control for confounding was strong in many of the studies used, some of the extrapolations are from subpopulations (eg, Mexican American) and our results are predicated on the generalizability of exposure-outcome relationships to European populations. Many of the exposure-outcome relationships used to extrapolate disease burden were log-linear and therefore had a supralinear component, though nonmonotonic relationships may also exist, just as they have been identified in animal studies. Finally, the extrapolation of attributable ADHD from a cross-sectional study bears some emphasis. While current exposures could be a proxy for exposures earlier in development, it is unlikely that ADHD is caused by exposure occurring at the time of diagnosis. Using the prospective studies would have presented the same weakness as our extrapolation for ASD in that the prospective studies of ADHD only look at symptoms rather than diagnosis of ADHD.

The strength of the approach taken includes the transparent use of available data to define dose-related outcomes and the distribution of exposures in EU countries, and such estimates will become more precise as better evidence becomes available. The causal attribution is supported by experimental data, and judgment in regard to reference levels, impact of covariates, and steepness of the dose-dependence of the outcomes was based on consensus among the authors. Likewise, biomarker data were not available for all EU countries, and judgment was used in extrapolating to the EU as a whole. By this approach, the authors attempted to avoid underestimating the burden of disease simply because of insufficient or lacking data (32). On the other hand, the calculations could not take into account potential differences between exposure levels in the member states.

A previous, independent effort to calculate the EU costs due to environmentally attributable intellectual disability estimated that these costs were $61.9 billion (27) based on the effects of lead and methylmercury poisoning only. Our calculated costs associated with several industrial chemicals are of the same order of magnitude. These estimates are likely to be additive rather than duplicative and testify to the substantial societal impact of cognitive deficits.

While endocrine disruption is defined generally as chemical disruption of endocrine systems (92), the exact mechanisms of neurotoxic effects are usually not known in detail. For all of the substances reviewed in this study, more than one mechanism is likely. However, disruption of thyroid hormone action is a commonality among the substances we included in the current analysis. This is important because the strength of the data linking thyroid disruption to cognitive and neurobehavioral disorders (4–7) provides confidence in our analysis. However, the fact remains that these chemicals are known to exert effects also through other pathways and it is not clear which is the most important. Proof of mechanism in humans is difficult if not impossible to establish, and the authors therefore relied on the EU definition of an EDC and a judgment based on weight of evidence and plausibility. Again, it bears emphasis that the exposure-outcome relationships extrapolated to disease burden are but a subset with the greatest evidence of the EDCs for which evidence of developmental neurotoxicity has been identified. Our calculations therefore suggest that prevention of EDC exposure would result in substantial societal benefits.

Acknowledgments

Research reported in this publication was supported by the Endocrine Society, the John Merck Fund, the Broad Reach Foundation, and the Oak Foundation. The funders and supporters had no role in the writing of the manuscript or the decision to submit it for publication. We thank Charles Persoz, Robert Barouki and Marion Le Gal of the French National Alliance for Life Sciences and Health, and Lindsey Marshall, Bilal Mughal and Bolaji Seffou of the UMR 7221 Paris for providing technical and logistical support throughout the project.

Address all correspondence and requests for reprints to: Leonardo Trasande, MD, MPP, Associate Professor, Department of Pediatrics, NY University School of Medicine, 227 East 30th Street Rm 109, NY, NY 10016,

leonardo.trasande@nyumc.org, phone 646–501-2520, fax 646–754-9688.

The authors have no conflicts or other disclosures to make.

This work was supported by .

References

1. **Grandjean P, Landrigan, P.J.** Neurobehavioural impact of developmental toxicity. *Lancet Neurol*. 2014;13:330–338.
2. **Grandjean P.** 2013 Only one chance. How Environmental Pollution Impairs Brain Development – and How to Protect the Brains of the Next Generation. New York: Oxford University Press
3. **Weiss B.** The intersection of neurotoxicology and endocrine disruption. *Neurotoxicology*. 2012;33:1410–1419.
4. **Chatonnet F, Flamant F, Morte B.** 2014 A temporary compendium of thyroid hormone target genes in brain. *Biochim Biophys Acta*
5. **Bernal J.** Thyroid hormone receptors in brain development and function. *Nat Clin Pract Endocrinol Metab*. 2007;3:249–259.
6. **Zoeller RT, Rovet J.** Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. *Journal of neuroendocrinology*. 2004;16:809–818.
7. **Demeneix B.** Losing our minds : chemical pollution and the mental health of future generations. Oxford series in behavioral neuroendocrinology, Oxford University Press, 2014.
8. **Wise A, Parham F, Axelrad DA, Guyton KZ, Portier C, Zeise L, Zoeller RT, Woodruff TJ.** Upstream adverse effects in risk assessment: A model of polychlorinated biphenyls, thyroid hormone disruption and neurological outcomes in humans. *Environmental Research*. 2012;117:90–99.
9. **Brown AS, Surcel H-M, Hinkka-Yli-Salomäki S, Cheslack-Postava K, Bao Y, Sourander A.** Maternal thyroid autoantibody and elevated risk of autism in a national birth cohort. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2015;57:86–92.
10. **Yau V, Lutsky M, Yoshida C, Lasley B, Kharrazi M, Windham G, Gee N, Croen L.** 2014 Prenatal and Neonatal Thyroid Stimulating Hormone Levels and Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders*.:1–12.
11. **Berbel P, Navarro D, Román GC.** 2014 An evo-devo approach to thyroid hormones in cerebral and cerebellar cortical development: Etiological implications for autism. Frontiers in Endocrinology 5.
12. **Andersen SL, Laurberg P, Wu CS, Olsen J.** Attention deficit hyperactivity disorder and autism spectrum disorder in children born to mothers with thyroid dysfunction: a Danish nationwide cohort study. *BJOG: An International Journal of Obstetrics, Gynaecology*. 2014;121:1365–1374.
13. **Boas M, Feldt-Rasmussen U, Main KM.** Thyroid effects of endocrine disrupting chemicals. *Mol. Cell. Endocrinol.* 2012;355:240–248.
14. **Bergman A, Heindel JJ, Jobling S, Kidd KA, Zoeller RT.** 2013 State of the Science of Endocrine Disrupting Chemicals 2012. In: United National Environment Programme and Worl Health Organization
15. **Elsabbagh M, Divan G, Koh YJ, Kim YS, Kauchali S, Marcin C, Montiel-Nava C, Patel V, Paula CS, Wang C, Yasamy MT, Fombonne E.** Global prevalence of autism and other pervasive developmental disorders. *Autism research : official journal of the International Society for Autism Research*. 2012;5:160–179.
16. **Baxter AJ, Brugha TS, Erskine HE, Scheurer RW, Vos T, Scott JG.** The epidemiology and global burden of autism spectrum disorders. *Psychol Med*. 2014:1–13.
17. **Willcutt EG.** The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. *Neurotherapeutics : the journal of the American Society for Experimental NeuroTherapeutics*. 2012;9:490–499.
18. **Landrigan PJ.** What causes autism? Exploring the environmental contribution. *Curr Opin Pediatr*. 2010;22:219–225.
19. **Bouchard MF, Bellinger DC, Wright RO, Weisskopf MG.** Attention-Deficit/Hyperactivity Disorder and Urinary Metabolites of Organophosphate Pesticides. *Pediatrics*. 125:e1270–1277.
20. **Braun JM, Kahn RS, Froehlich T, Auinger P, Lanphear BP.** Exposures to Environmental Toxicants and Attention Deficit Hyperactivity Disorder in US Children. *Environmental Health Perspectives*. 2006;114:1904.
21. **Braun JM, Kalkbrenner AE, Just AC, Yolton K, Calafat AM, Sjodin A, Hauser R, Webster GM, Chen A, Lanphear BP.** Gestational exposure to endocrine-disrupting chemicals and reciprocal social, repetitive, and stereotypic behaviors in 4- and 5-year-old children: the HOME study. *Environ Health Perspect*. 2014;122:513–520.
22. **Marks AR, Harley K, Bradman A, Kogut K, Barr DB, Johnson C, Calderon N, Eskenazi B.** Organophosphate pesticide exposure and attention in young Mexican-American children: the CHAMACOS study. *Environ Health Perspect*. 2010;118:1768–1774.
23. **Gascon M, Vrijheid M, Martinez D, Forns J, Grimalt JO, Torrent M, Sunyer J.** 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;37:605–611.
24. **Braun JM, Kahn RS, Froehlich T, Auinger P, Lanphear BP.** Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children. *Environ Health Perspect*. 2006;114:1904–1909.
25. **Buescher AS, Cidav Z, Knapp M, Mandell DS.** COsts of autism spectrum disorders in the united kingdom and the united states. *JAMA Pediatrics*. 2014;168:721–728.
26. **Le H, Hodgkins P, Postma M, Kahle J, Sikirica V, Setyawan J, Erder MH, Doshi J.** Economic impact of childhood/adolescent ADHD in a European setting: the Netherlands as a reference case. *Eur Child Adolesc Psychiatry*. 2014;23:587–598.
27. **Bartlett ES, Trasande L.** Economic impacts of environmentally attributable childhood health outcomes in the European Union. *European journal of public health*. 2014;24:21–26.
28. **Bouchard MF, Chevrier J, Harley KG, Kogut K, Vedar M, Calderon N, Trujillo C, Johnson C, Bradman A, Barr DB, Eskenazi B.** 2011 Prenatal Exposure to Organophosphate Pesticides and IQ in 7-Year-Old Children. *Environ Health Perspect*. 119.
29. **Eskenazi B, Chevrier J, Rauch SA, Kogut K, Harley KG, Johnson C, Trujillo C, Sjodin A, Bradman A.** In utero and childhood polybrominated diphenyl ether (PBDE) exposures and neurodevelopment in the CHAMACOS study. *Environ Health Perspect*. 2013;121:257–262.
30. **Chen A, Yolton K, Rauch SA, Webster GM, Hornung R, Sjodin A, Dietrich KN, Lanphear BP.** 2014 Prenatal Polybrominated Diphenyl Ether Exposures and Neurodevelopment in U.S. Children through 5 Years of Age: The HOME Study. *Environ Health Perspect*.
31. **Bellanger et al..** 2013 Economic benefits of methylmercury exposure control in Europe: monetary value of neurotoxicity prevention Environmental Health 12.
32. **Pruss-Ustun A, Vickers C, Haefliger P, Bertollini R.** Knowns and unknowns on burden of disease due to chemicals: a systematic review. *Environmental health : a global access science source*. 2011;10:9.
33. **Intergovernmental Panel on Climate Change.** 2005 Guidance Notes for Lead Authors of the IPCC Fourth Assessment Report on Addressing Uncertainties. Available at http://www.ipcc.ch/meetings/ar4-workshops-express-meetings/uncertainty-guidance-note.pdf (Accessed 12 May 2014).
34. **Boas M, Frederiksen H, Feldt-Rasmussen U, Skakkebaek NE, Hegedus L, Hilsted L, Juul A, Main KM.** Childhood exposure to phthalates: associations with thyroid function, insulin-like growth factor I, and growth. *Environ Health Perspect*. 2010;118:1458–1464.
35. **Trasande L, Zoeller RT, Hass U, Kortenkamp A, Grandjean P, Myers JP, DiGangi J, Bellanger M, Hauser R, Legler J, Skakkebaek NE, Heindel JJ.** 2015 Estimating Burden and Disease Costs of Ex-

posure to Endocrine Disruptor Chemicals in the European Union. J Clin Endocrinol Metab preliminarily accepted
36. **Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schunemann HJ, Edejer T, Varonen H, Vist GE, Williams JW, Jr., Zaza S.** Grading quality of evidence and strength of recommendations. *Bmj*. 2004;328:1490.
37. **Schunemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, Williams JW, Jr., Kunz R, Craig J, Montori VM, Bossuyt P, Guyatt GH.** Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *Bmj*. 2008;336:1106–1110.
38. **Hass U, Christiansen S, Axelstad M, Boberg J, Andersson A-M, Skakkebaek NE, Bay K, Holbech H, Kinnberg KL, Bjerregaard P.** 2012 Evaluation of 22 SIN List 2.0 substances according to the Danish proposal on criteria for endocrine disrupters. Available at http://eng.mst.dk/media/mst/67169/SIN%20report%20and%20Annex.pdf (Accessed 12 May 2014).
39. **Herbstman JB, SjÃ¶din A, Kurzon M, Lederman SA, Jones RS, Rauh V, Needham LL, Tang D, Niedzwiecki M, Wang RY, Perera F.** Prenatal Exposure to PBDEs and Neurodevelopment. Environ Health Perspect 118.
40. **Eurostat.** 2014 Births in European Countries, 2010 Available at http://epp.eurostat.ec.europa.eu/portal/page/portal/population (Accessed 3 October 2014).
41. **Engel SM, Wetmur J, Chen J, Zhu C, Barr DB, Canfield RL, Wolff MS.** Prenatal exposure to organophosphates, paraoxonase 1, and cognitive development in childhood. *Environ Health Perspect*. 2011;119:1182–1188.
42. **Bellinger DC.** A strategy for comparing the contributions of environmental chemicals and other risk factors to neurodevelopment of children. *Environ Health Perspect*. 2012;120:501–507.
43. **Miodovnik A, Engel SM, Zhu C, Ye X, Soorya LV, Silva MJ, Calafat AM, Wolff MS.** Endocrine disruptors and childhood social impairment. *Neurotoxicology*. 2011;32:261–267.
44. **Wigham S, McConachie H, Tandos J, Le Couteur AS.** The reliability and validity of the Social Responsiveness Scale in a UK general child population. *Research in Developmental Disabilities*. 2012;33:944–950.
45. **Eurostat.** 2014 People by age group, European Union. Available at http://epp.eurostat.ec.europa.eu/tgm/refreshTableAction.do;jsessionid=9ea7d07d30de780141256da541caa795f04b252b7 (Accessed 25 August 2014).
46. **Levin M.** The occurrence of lung cancer in man. *Acta Unio Int Contra Cancrum*. 1953;9:531–541.
47. **Zhang J, Yu KF.** What's the relative risk?: A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA*. 1998;280:1690–1691.
48. **Chen A, Yolton K, Rauch SA, Webster GM, Hornung R, Sjodin A, Dietrich KN, Lanphear BP.** Prenatal Polybrominated Diphenyl Ether Exposures and Neurodevelopment in U.S. Children through 5 Years of Age: The HOME Study. *Environ Health Perspect*. 2014;122:856–862.
49. **Eskenazi B, Chevrier J, Rauch SA, Kogut K, Harley KG, Johnson C, Trujillo C, Sjodin A, Bradman A.** In utero and childhood polybrominated diphenyl ether (PBDE) exposures and neurodevelopment in the CHAMACOS study. *Environ Health Perspect*. 2013;121:257–262.
50. **Herbstman JB, Sjodin A, Kurzon M, Lederman SA, Jones RS, Rauh V, Needham LL, Tang D, Niedzwiecki M, Wang RY, Perera F.** Prenatal exposure to PBDEs and neurodevelopment. *Environ Health Perspect*. 2010;118:712–719.
51. **Abdelouahab N, Suvorov A, Pasquier JC, Langlois MF, Praud JP, Takser L.** Thyroid disruption by low-dose BDE-47 in prenatally exposed lambs. *Neonatology*. 2009;96:120–124.
52. **Brasseur C, Pirard C, Scholl G, De Pauw E, Viel JF, Shen L, Reiner EJ, Focant JF.** Levels of dechloranes and polybrominated diphenyl ethers (PBDEs) in human serum from France. *Environ Int*. 2014;65:33–40.
53. **Lenters V, Thomsen C, Smit LA, Jonsson BA, Pedersen HS, Ludwicki JK, Zviezdai V, Piersma AH, Toft G, Bonde JP, Becher G, Vermeulen R, Heederik D.** Serum concentrations of polybrominated diphenyl ethers (PBDEs) and a polybrominated biphenyl (PBB) in men from Greenland, *Poland and Ukraine*. *Environ Int*. 2013;61:8–16.
54. **Gari M, Grimalt JO.** Inverse age-dependent accumulation of decabromodiphenyl ether and other PBDEs in serum from a general adult population. *Environ Int*. 2013;54:119–127.
55. **Eriksson P, Jakobsson E, Fredriksson A.** Brominated flame retardants: a novel class of developmental neurotoxicants in our environment? *Environ Health Perspect*. 2001;109:903–908.
56. **USEPA.** 2014 Toxicological Review of 2,2′,4,4′-TETRABROMODIPHENYL ETHER (BDE-47). Available at http://www.epa.gov/iris/toxreviews/1010tr.pdf (Accessed 3 October 2014).
57. **European Food Safety Authority.** 2014 Scientific Opinion on Polybrominated Diphenyl Ethers (PBDEs) in Food. Available at http://www.efsa.europa.eu/en/efsajournal/doc/2156.pdf (Accessed 3 October 2014).
58. **Shimizu R, Yamaguchi M, Uramaru N, Kuroki H, Ohta S, Kitamura S, Sugihara K.** Structure-activity relationships of 44 halogenated compounds for iodotyrosine deiodinase-inhibitory activity. *Toxicology*. 2013;314:22–29.
59. **de Escobar GM, Ares S, Berbel P, Obregon MJ, del Rey FE.** The changing role of maternal thyroid hormone in fetal brain development. *Semin Perinatol*. 2008;32:380–386.
60. **Oerbeck B, Sundet K, Kase BF, Heyerdahl S.** Congenital hypothyroidism: no adverse effects of high dose thyroxine treatment on adult memory, attention, and behaviour. *Arch Dis Child*. 2005;90:132–137.
61. **Gee JR, Hedge JM, Moser VC.** Lack of alterations in thyroid hormones following exposure to polybrominated diphenyl ether 47 during a period of rapid brain development in mice. *Drug and chemical toxicology*. 2008;31:245–254.
62. **Costa LG, de Laat R, Tagliaferri S, Pellacani C.** A mechanistic view of polybrominated diphenyl ether (PBDE) developmental neurotoxicity. *Toxicology letters*. 2014;230:282–294.
63. **Bouchard MF, Chevrier J, Harley KG, Kogut K, Vedar M, Calderon N, Trujillo C, Johnson C, Bradman A, Barr DB, Eskenazi B.** Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. *Environ Health Perspect*. 2011;119:1189–1195.
64. **Rauh VA, Garfinkel R, Perera FP, Andrews HF, Hoepner L, Barr DB, Whitehead R, Tang D, Whyatt RW.** 2006 Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. Pediatrics
65. **De Angelis S, Tassinari R, Maranghi F, Eusepi A, Di Virgilio A, Chiarotti F, Ricceri L, Venerosi Pesciolini A, Gilardi E, Moracci G, Calamandrei G, Olivieri A, Mantovani A.** Developmental exposure to chlorpyrifos induces alterations in thyroid and thyroid hormone levels without other toxicity signs in CD-1 mice. *Toxicological sciences : an official journal of the Society of Toxicology*. 2009;108:311–319.
66. **Jeong SH, Kim BY, Kang HG, Ku HO, Cho JH.** Effect of chlorpyrifos-methyl on steroid and thyroid hormones in rat F0- and F1-generations. *Toxicology*. 2006;220:189–202.
67. **Levin ED, Addy N, Baruah A, Elias A, Christopher NC, Seidler FJ, Slotkin TA.** Prenatal chlorpyrifos exposure in rats causes persistent behavioral alterations. *Neurotoxicology and teratology*. 2002;24:733–741.
68. **Berbel P, Auso E, Garcia-Velasco JV, Molina ML, Camacho M.** Role of thyroid hormones in the maturation and organisation of rat barrel cortex. *Neuroscience*. 2001;107:383–394.
69. **Engel S, Wetmur J, Chen J, Zhu C, Barr D, Canfield R, Wolff M.** Prenatal exposure to organophosphates, paraoxonase 1, and cognitive development in childhood. *Environ Health Perspect*. 2011;119:1182.

70. **Rosenberg RE, Law JK, Yenokyan G, McGready J, Kaufmann WE, Law PA.** Characteristics and concordance of autism spectrum disorders among 277 twin pairs. *Arch Pediatr Adolesc Med*. 2009; 163:907–914.
71. **National Academy of Sciences Committee on Developmental Toxicology 2000. Scientific Frontiers in Developmental Toxicology and Risk Assessment. In. Washington, DC**
72. **Roman GC, Ghassabian A, Bongers-Schokking JJ, Jaddoe VW, Hofman A, de Rijke YB, Verhulst FC, Tiemeier H.** Association of gestational maternal hypothyroxinemia and increased autism risk. *Annals of neurology*. 2013;74:733–742.
73. **Kalkbrenner AE, Schmidt RJ, Penlesky AC.** 2014 Environmental Chemical Exposures and Autism Spectrum Disorders: A Review of the Epidemiological Evidence. Current problems in pediatric and adolescent health care
74. **Toppari J, Virtanen HE, Main KM, Skakkebaek NE.** Cryptorchidism and hypospadias as a sign of testicular dysgenesis syndrome (TDS): environmental connection. Birth defects research. *Part A, Clinical and molecular teratology*. 2010;88:910–919.
75. **O'Connor JC, Frame SR, Ladics GS.** Evaluation of a 15-day screening assay using intact male rats for identifying steroid biosynthesis inhibitors and thyroid modulators. *Toxicological sciences : an official journal of the Society of Toxicology*. 2002;69:79–91.
76. **Meeker JD, Ferguson KK.** 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*. 2011;119:1396–1402.
77. **Weiss RE, Stein MA, Trommer B, Refetoff S.** Attention-deficit hyperactivity disorder and thyroid function. *J Pediatr*. 1993;123:539–545.
78. **Refetoff S, Dumitrescu AM.** Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. *Best Pract Res Clin Endocrinol Metab*. 2007;21:277–305.
79. **McDonald MP, Wong R, Goldstein G, Weintraub B, Cheng SY, Crawley JN.** Hyperactivity and learning deficits in transgenic mice bearing a human mutant thyroid hormone beta1 receptor gene. *Learn Mem*. 1998;5:289–301.
80. **Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ.** Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med*. 1999;341:549–555.
81. **Akaike M, Kato N, Ohno H, Kobayashi T.** Hyperactivity and spatial maze learning impairment of adult rats with temporary neonatal hypothyroidism. *Neurotoxicol Teratol*. 1991;13:317–322.
82. **Kiguchi M, Fujita S, Oki H, Shimizu N, Cools AR, Koshikawa N.** Behavioural characterisation of rats exposed neonatally to bisphenol-A: responses to a novel environment and to methylphenidate challenge in a putative model of attention-deficit hyperactivity disorder. *Journal of neural transmission (Vienna, Austria : 1996)*. 2008;115:1079–1085.
83. **Sazonova NA, DasBanerjee T, Middleton FA, Gowtham S, Schuckers S, Faraone SV.** Transcriptome-wide gene expression in a rat model of attention deficit hyperactivity disorder symptoms: rats developmentally exposed to polychlorinated biphenyls. American journal of medical genetics. *Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 2011;156b:898–912.
84. **Trasande L, Liu Y.** Reducing the staggering costs of environmental disease in children, estimated at $76.6 billion in 2008. *Health Aff (Millwood)*. 2011;30:863–870.
85. **Attina TM, Trasande L.** Economic costs of childhood lead exposure in low- and middle-income countries. *Environ Health Perspect*. 2013;121:1097–1102.
86. **Spadaro JV, Rabl A.** Global health impacts and costs due to mercury emissions. *Risk Anal*. 2008;28:603–613.
87. **UNEP Global Alliance to Eliminate Lead in Paints. Available at http://www.chem.unep.ch/Lead in paint/default.htm (Accessed 14 December 2010).**
88. **UNEP Partnership on Clean Fuels and Vehicles. Available at http://www.unep.org/pcfv/about/bkground.asp (Accessed 14 December 2010).**
89. **Trasande L, Schechter CB, Haynes KA, Landrigan PJ.** Mental retardation and prenatal methylmercury toxicity. *Am J Ind Med*. 2006;49:153–158.
90. **Engel SM, Miodovnik A, Canfield RL, Zhu C, Silva MJ, Calafat AM, Wolff MS.** Prenatal phthalate exposure is associated with childhood behavior and executive functioning. *Environ Health Perspect*. 2010;118:565–571.
91. **Taylor PN, Okosieme OE, Murphy R, Hales C, Chiusano E, Maina A, Joomun M, Bestwick JP, Smyth P, Paradice R, Channon S, Braverman LE, Dayan CM, Lazarus JH, Pearce EN.** 2014 Maternal perchlorate levels in women with borderline thyroid function during pregnancy and the cognitive development of their offspring; Data from the Controlled Antenatal Thyroid Study. J Clin Endocrinol Metab:jc20141901.
92. **Damstra T, Barlow S, Bergman A, Kavlock RJ, van der Kraak G eds..** 2002 Global assessment of the state-of-the-science of endocrine disruptors. Geneva, Switzerland: World Health Organization