Universiteit Utrecht

Institute *for* Risk Assessment Sciences

# Putting a price on your exposed brain

## A case-study towards prenatal exposure to polybrominated diphenyl ethers (PBDEs), organophosphate pesticides (OPs) and associated socio-economic cost of IQ loss in the Netherlands

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**Samenvatting**

Gebromeerde difenylethers (PBDEs) en organofosfaat pesticiden (OPs) zijn twee voorbeelden van hormoonverstorende chemicaliën ('Endocrine Disrupting Chemicals' - EDCs), die worden geassocieerd met negatieve effecten op de hersenontwikkeling bij kinderen.

In deze studie is de socio-economische impact voor de Nederlandse samenleving berekend in verband met het mogelijk dalen van de IQ door blootstelling aan PBDEs en OPs tijdens de zwangerschap.

Studies met kinderen in de Verenigde Staten hebben een rekenkundige relatie vastgesteld voor de verlaging van de IQ en de mate van blootstelling aan PBDEs en OPs tijdens de zwangerschap. Deze relaties zijn toegepast op de gegevens van blootstellingswaarden in zwangere Nederlandse vrouwen in de periode 2000 -2006.

De Nederlandse blootstellingswaarden voor PBDEs waren gemiddeld een ordegrootte lager dan die in de Verenigde Staten. Op grond van onze berekeningen kan toch verwacht worden dat in de hoogst blootgestelde 5% van de pasgeborenen in Nederland eveneens een verlaging van de IQ met 1.0 punt (95% betrouwbaarheidsinterval (B.I.): 0.02 – 1.9) is opgetreden. Omdat deze PBDEs persistent zijn in het milieu en de mens is de verwachting dat deze stoffen nog steeds negatieve invloed op de hersenontwikkeling in Nederland kunnen hebben bij een deel van de kinderen.

De Nederlandse blootstellingwaarden voor OPs, zijn juist 3 tot 5 maal hoger dan de gemiddelde waarden in de Verenigde Staten. Toepassing van de Nederlandse waarden op de Amerikaanse blootstellings-respons relatie gaf aan dat een IQ daling van 5.1 punten (95% B.I. 2.0 – 8.1) voor kinderen in de 5% hoogst blootgestelde groep mogelijk is. IQ verlies is ook berekend voor enkele lager blootgestelde groepen, namelijk die tussen het 50$^{e}$ en 75$^{e}$ percentiel (1.7 IQ punten verlies; 95% B.I. 0.7 – 2.7) en 75$^{e}$ en 95$^{e}$ percentiel (3.1 IQ punten verlies; 95% B.I. 1.2 – 5.0).

Wanneer dit geschatte IQ verlies van de Nederlandse bevolking uitgedrukt wordt in sociaal-economische kosten, wordt een jaarlijks verlies verwacht van € 100 miljoen (95% B.I. 0 – 200 miljoen) en € 2.7 miljard (95% B.I. 1.1 – 4.4 miljard) voor respectievelijk PBDEs en OPs bij deze blootstellingsconcentraties. Daarnaast kunnen deze hormoonverstorende stoffen waarschijnlijk ook bijdragen aan andere negatieve gezondheidseffecten zoals stofwisselingsziekten, (neuro)gedragsproblemen, bepaalde hormoongevoelige tumoren en afwijkingen aan het mannelijk voortplantingsorgaan.

Aanbevolen wordt dat de Nederlandse overheid meer maatregelen treft om de blootstelling aan hormoonverstorende stoffen verder te reduceren. Hierdoor zou de gezondheid van toekomstige generaties beter beschermd worden en tegelijkertijd ook de (in)directe sociaal-economische kosten voor de Nederlandse samenleving worden verminderd.

**Summary**

Polybrominated biphenyls (PBDEs) and organophosphate pesticides (OPs) are two classes of Endocrine Disrupting Chemicals (EDCs) that have been associated with adverse effects on neurocognitive development in children.

In this study, we quantified the annual socio-economic costs of prenatal exposure resulting in the loss of IQ points in the Dutch population.

We used existing exposure-response relationships (ERRs) for PBDE- and OP-related IQ loss that were reported from several recent US cohort studies. These ERRs were applied to typical exposure levels of PBDEs and OPs measured in pregnant Dutch women in the beginning of the 21$^{st}$ century.

For PBDEs, it was found that average exposure levels in the Netherlands are typically one order of magnitude lower compared to those in the US. However, for 5% of the highest exposed Dutch population, an average cognitive loss of 1.0 IQ point (95% C.I. 0.02 – 1.9) was estimated per new-born.

For OPs, the application of ERRs to existing Dutch exposure values resulted in a loss 5.1 IQ points (95% C.I. 2.0 – 8.1) for new-born babies in the highest 5% exposure group. Average OPs levels in the Dutch pregnant women were 3 to 5 times higher than average US exposure levels. Therefore, the loss of IQ points was also calculated for the exposure group between the 50$^{th}$ and 75$^{th}$ percentile (1.7 IQ points loss; 95% C.I. 0.7 – 2.7) and 75$^{th}$ and 95$^{th}$ percentile (3.1 IQ point loss; 95% C.I. 1.2 – 5.0).

When the expected loss of IQ points in the population is expressed in socio-economic impacts, our calculations suggests that PBDE- and OPs-related IQ loss leads to societal (indirect) costs in the Netherlands of respectively € 100 million (95% C.I. 0 – 200 million) and € 2.7 billion (95% C.I. 1.1 – 4.4 billion) annually. These results were in line with results of a recent study, which calculated socio-economic costs of these compounds for the EU.

Bearing in mind that EDCs are also likely to contribute to other adverse health effects such as neurobehavioral disorders, metabolic diseases, certain hormone dependent cancers, and male reproductive disorders, it is recommended to implement measures to reduce and prevent EDC exposure in order to first of all protect future generations, but also limit the societal costs.

## Introduction

There is increasing toxicological and epidemiological evidence that certain chemicals can have the ability to interfere with the endocrine system in humans and wildlife. Exposure to such Endocrine Disrupting Chemicals (EDCs) in humans has been related to a whole spectrum of diseases and deficits, including metabolic diseases, certain hormone dependent tumors, neurobehavioral deficits and male reproductive deficits. Well-known examples of EDCs include polychlorinated biphenyls (PCBs), polybrominated diphenylethers (PBDEs), organophosphorus pesticides (OPs), phthalates, bisphenol-A (BPA) and chlorinated dioxins.

Recently, various studies have demonstrated that continuing exposure to EDCs may lead to high societal costs in the EU if decreased fertility, congenital malformations, hormone related cancers, loss of intelligence, attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), diabetes and obesity are taking into account (Bellanger, Demeneix, Grandjean, Zoeller, & Trasande, 2015; Hauser et al., 2015; HEAL, 2014; Ing-Marie et al., 2014; Legler et al., 2015; Trasande et al., 2015). Focusing on male reproductive health disorders only, The Nordic Council has now calculated the cost in the EU-28 to be about € 600 million (€ 59-1200 million) per year of exposure (Ing-Marie et al., 2014). When the various health impacts of EDCs were combined, the best-cost estimates for their health impacts in the EU-28 ranged from € 13 to 31 billion (HEAL, 2014) to € 157 billion on an annual basis (Trasande et al., 2015). These differences in costs were mainly caused by the types of health effects modeled, methodology applied (based on either dose-response relationships or estimated etiological fractions of the adverse health effects), and to which extent indirect and intangible costs were included in the analysis. However, in spite of different methodologies the costs arising from neurological disorders affecting child brain development and behavior contributed heavily to the total costs. For example, in the calculations of the Health and Environment Alliance (HEAL), neurobehavioral deficits accounted for more than one third of the total estimated costs (HEAL, 2014). Moreover, the group of scientists in the consortium of Trasande calculated that neurobehavioral deficits accounted for over 80% of total costs in the EU (Trasande et al., 2015). A noticeable dissimilarity between both studies is that the latter also included the costs that were associated with loss of cognition, which explains the difference in cost estimates.

Due to the critical role of hormones in directing differentiation in many tissues, the developing organism is particularly vulnerable for fluctuations in the timing or intensity of exposure to chemicals with hormonal (or anti-hormonal) activity (Barlow et al., 1999; Bigsby et al., 1999; Landrigan et al., 1999). Endocrine disruption in critical and sensitive time windows during the development of the fetus, may result in irreversible effects on the differentiating tissues, including those of the brain (Bigsby et al., 1999). In this respect, there is general consensus that the vulnerability to endocrine active chemicals is greatest during the embryonic and early fetal life, especially in the first trimester of pregnancy (Grandjean & Landrigan, 2006; Grandjean & Landrigan, 2014; Rice & Barone Jr., 2000; Rodier, 1994).

Clear evidence for loss of cognition due to prenatal exposure to EDCs has -so far- been reported for at least three groups of substances: PBDEs, OPs, and phthalates. (Neuro)toxic effects of these compounds are already known for decades from experimental studies, but also from occupational exposure situations. Beside the evidence from toxicological studies, there is now increasing evidence for these effects at population levels that provides biological plausibility for these epidemiological studies. Exposure response relations (ERRs) have been described in recent epidemiological studies, which relate systemic maternal exposure levels of OPs, PBDEs or phthalates directly to IQ loss in early childhood (Bouchard et al., 2011; Chen et al., 2014; Engel et al., 2011; Eskenazi et al., 2013; Eskenazi et al., 2014; Factor-Litvak et al., 2014; Herbstman et al., 2010). In addition, postnatal exposure to PBDEs has also shown to be associated with decrements in IQ and behavioral outcomes (Eskenazi et al., 2013) However, to our knowledge no negative association between postnatal exposure to OPs and IQ loss has been reported (Bouchard et al., 2011). Based on the above observations we calculated to which extent prenatal exposure to PBDEs and OPs in the beginning of the 21$^{st}$ century could have negatively influenced the IQ in early childhood in the Dutch population.

PBDEs are a group of organobromine compounds with a variable degree of bromination and have been used as flame retardant, for instance in textiles, furniture, plastics and electronics. Although PBDEs are currently banned in the EU as well as under the international Stockholm Convention, these compounds are still omnipresent in the environment, human food chain as well as in older household products. As a result, the general population is still continuously exposed via ingestion of household dust and food products of animal origin.
OPs are a wide group of over 100 organophosphorus compounds, which all have a similar mode of action by inhibiting acetylcholinesterase in the nervous system. OPs are used as insecticides to control insect vectors, which are found in food and commercial crops, infestations in domestic and commercial buildings, and in man or domestic animals. Examples of OPs include chlorpyrifos, malathion and parathion. In contrast to PBDEs, OPs are not very persistent in the environment because these biocides break down easily. At present, not all OPs are banned, and the Dutch population is generally exposed via ingestion of residues found on fruit and vegetables that may originate from outside the EU.

The aim of the current report is to determine a socio-economic cost estimate for PBDE- and OPs-associated IQ loss in the Dutch population. We used ERRs for PBDE- and OPs-related IQ loss that were reported from the US and applied these to typical exposure levels in the Dutch population in the beginning of the 21$^{st}$ century. Next, we quantified the socio-economic cost due to the total decrease of IQ points in the Dutch population.

## Methods

*Selection of exposure-response relationships (ERRs)*

ERRs for PBDE-associated IQ loss are available from three different US longitudinal birth cohort studies, which demonstrated neurodevelopmental effects of prenatal and early-life exposure to PBDEs. (Chen et al., 2014; Eskenazi et al., 2013; Herbstman et al., 2010). All these studies focused on cognitive functioning by measuring outcome on verbal comprehension, perceptual reasoning, working memory and processing speed, which combined provide the Full-Scale IQ (FSIQ). The PBDE levels measured in serum of mothers, their children and/or cord blood were the basis for the ERRs presented in these studies. For OP-associated IQ loss, two US publications were also available, which reported ERRs that could be used for our Dutch study (Bouchard et al., 2011; Engel et al., 2011). In contrast to the ERRs of the PBDEs, these OPs were not measured directly in blood or serum, but quantified by the presence of metabolites in maternal urine. These urinary OP-metabolites were classified as dimethylphosphate (DMP) and diethylphosphate (DEP) metabolites. In both US studies, the sum of DEP and DMP metabolites provided the total dialkylphosphate (DAP) metabolites level that were related to cognitive development and associated development of IQ in early childhood (6-9 years). These urinary DAP metabolites are generally regarded as good indicators of human OP exposure, although their levels may also reflect exposure to OP breakdown products in the environment and food, as well as the contribution of some industrial chemicals and drugs (Barr & Needham, 2002).

The US ERRs for respectively PBDE- and OP-associated FSIQ loss are presented in table 1 and 2, which we used for our own calculations. The 95% Confidence Interval (95% C.I.) is shown for each ERR. We assumed that the intellectual development in early childhood and prenatal ERRs for both compounds are not different for the US and Dutch populations. Furthermore, it should be recognized that these US studies have some (minor) differences in methodology, e.g. version of cognition test to measure FSIQ in children, age of testing of children, types of PBDE congeners or OP-urine metabolites taken for association, medium of PBDE measurement and analytical- and statistical methodology used (not shown). From the studies of Herbstman et al., and the study of Engel et al., two different ERRs are shown for respectively different PBDE-congeners or group of OP-metabolites measured in urine. It should be noted that both an ERR for PBDE- and OP-associated IQ loss was derived from the same birth cohort in California (CHAMACOS). The authors conclude that the observed associations appear to be independent from each other (Bouchard et al., 2011; Eskenazi et al., 2013).

When comparing the ERRs for PBDE exposure and IQ loss, the three studies show formulas with a similar effect, confirming that the strength of evidence is high. Exposure levels of individual congeners are to a large extent correlated, as people are invariable exposed to PBDE mixtures instead of single congeners. The ERR from the HOME cohort was selected for further calculations of the loss of cognition (IQ) for the Dutch situation (Chen et al., 2014). This ERR is based on BDE-47 levels in maternal serum, for which reliable data were also available for Dutch pregnant women from a study in Northern part of the Netherlands (Meijer et al., 2008). The ERR determined by

**Table 1.** ERRs for PBDE exposure and loss of cognition, derived from three different US longitudinal birth cohort studies

| Cohort | Reference | N | Cognition test* and age of testing | ERR β (95% CI min; max) | Remark |
|---|---|---|---|---|---|
| **HOME (Ohio)** | Chen et al., 2014 | 309 | FSIQ (WPPSI-III), age 5 | -4.5 (-8.8; -0.1) /log10 prenatal maternal serum BDE-47 | |
| **CHAMACOS (California)** | Eskenazi et al., 2013 | 323 | FSIQ (WPPSI-IV), age 7 | -4.7 (-9.4; 0.1) /log10 prenatal maternal serum ∑4BDE** | Near significant ERR (p<0.1) |
| **WTC (New York)** | Herbstman et al., 2010 | 210 | FSIQ (WPPSI-R), age 4 and age 6 | -2.42 (-4.71; -0.12) /ln cord blood BDE-47 | ERR at age 4 |
| | | | | -3.4 (-6.59; -0.22) /ln cord blood BDE-153 | ERR at age 6 |

* FSIQ: Full Scale IQ.
WPPSI-III/IV/R: Wechsler Intelligence Scale for Children –Third, Fourth and Revised Edition
** ∑4BDE = sum of congeners BDE-47, -99, -100 and -153

**Table 2.** ERRs for OPs exposure and loss of cognition, derived from two different US longitudinal birth cohort studies

| Cohort | Reference | N | Cognition test* and age of testing | ERR β (95% CI min; max)** | Remark |
|---|---|---|---|---|---|
| **CHAMACOS (California)** | Bouchard et al., 2011 | 329 | FSIQ (WPPSI-IV), age 7 | -5.6 (-9.0; -2.2) / log 10 mean ∑DAP | mean DAP of two measurements <20 wks and >20 wks of gestation |
| **CEHS (New York)** | Engel et al., 2011 | 169 | FSIQ (WPPSI-III and WPPSI-IV), age 6-9 | -1.39 (-4.54; 1.77)/ log 10 ∑DAP – creatinine adjusted | one measurement at 26-28 wks |
| | | | | -2.89 (-6.15; 0.36) / log 10 ∑DEP – creatinine adjusted | |

* FSIQ: Full Scale IQ.
WPPSI-III/IV/R: Wechsler Intelligence Scale for Children –Third and Fourth Edition
**DAP: dialkyl phosphate metabolites (DAP=diethyl phosphate metabolites (DEP) + dimethyl phosphate metabolites (DMP))

Chen et al., (2014) also holds at lower concentrations of BDE-47 (3-10 ng/g lipid), corresponding to Dutch exposure levels. There was insufficient data on Dutch PBDE cord blood levels (N=12) to provide a reliable socio-economic cost estimate based on the ERR derived from the WTC cohort.

For OPs, the two US studies both find negative effects on cognition, however the CHAMACOS cohort provided an effect, which is about three times larger if compared to the CEHS cohort. This could be explained by the higher exposure levels in California compared to New York, as well as using a more reliable estimate of exposure (mean of two measurements instead of one measurement), lifestyle differences, or alternatively a possible different genetic susceptibility towards OPs exposure. Both ERRs are based upon maternal DAP and DEP metabolites in urine, for which reliable information on Dutch exposure levels (non-adjusted and adjusted for creatinine in urine) is available (Ye et al., 2008). Dutch exposure levels correspond to a large extent to the levels upon which these ERRs are based, making them suitable for further calculations of loss of cognition (IQ) in the Netherlands. For the final calculations only the ERR from the CHAMACOS cohort was used, because urinary levels in this study were closest to those observed in the Dutch population.

*Exposure levels of PBDEs and OPs in the Netherlands*

Information on typical PBDE exposure levels in the Netherlands has been derived from previous published serum PBDE levels from the prospective cohort study 'Groningen infant COMPARE' (Comparison of Exposure-Effect Pathways to Improve the Assessment of Human Health Risks of Complex Environmental Mixtures of Organohalogens) (Meijer et al., 2008; Roze et al., 2009). The Groningen infant COMPARE cohort is the only study of pregnant women in the Netherlands in which PBDEs have been measured in maternal serum and cord blood. Typical concentration levels for BDE-47 in maternal serum are presented in table 3. The average Dutch exposure levels are typically one order of magnitude lower than the average US exposure levels (Chen et al., 2014; Eskenazi et al., 2013; Herbstman et al., 2010). However, the ERRs determined in the US studies were still covering the higher part of the Dutch exposure range, noticeable those at the Dutch 95 percentile or higher.

**Table 3.** BDE-47 exposure levels in maternal serum of pregnant women (N=77) from the Groningen infant COMPARE study (Meijer et al., 2008). Detection frequency=100%.

| Congener (ng/g lipid) | Mean | Min. | Percentile | | | | | Max. |
|---|---|---|---|---|---|---|---|---|
| | | | 5th | 25th | 50th | 75th | 95th | |
| BDE-47 | 1.17 | 0.04 | 0.22 | 0.51 | 0.84 | 1.37 | 3.94 | 6.11 |

Information on prenatal OPs exposure was derived from the Generation R study, a population-based birth cohort study in the city of Rotterdam (Ye et al., 2008). From this cohort, 100 urine samples from women whose pregnancy resulted in a live birth, were randomly selected for analysis of OP metabolites. Results from measurements of six nonspecific DAP metabolites were reported as individual DMP and DEP metabolites. Again, this is the only study that measured systemic exposure to OPs in Dutch pregnant women.

The non-adjusted and creatinine-adjusted DEP, DMP and total DAP levels are presented in respectively table 4a and 4b. It should be noted that the median total DAP levels in the Dutch cohort are 3 to 5 times higher compared to median total DAP levels reported in the US CHAMACOS and CEHS cohort studies.

**Table 4a.** Non-adjusted levels of OPs metabolites in the urine of Dutch pregnant women (N=100) from the Generation R study (Ye et al., 2008).

| Metabolites (nmol/L) | Geometric Mean | Min. | Percentile | | | | | Max. |
|---|---|---|---|---|---|---|---|---|
| | | | 5th | 25th | 50th | 75th | 95th | |
| Total DMP | 157.0 | 16.7 | 30.5 | 85.4 | 179.0 | 310.0 | 584.0 | 1540.0 |
| Total DEP | 19.7 | 1.3 | 3.2 | 9.6 | 19.2 | 35.7 | 160.0 | 350.0 |
| **Total DAP** | **183.0** | **23.1** | **34.2** | **97.3** | **200.0** | **370.0** | **659.0** | **1890.0** |

**Table 4b.** Creatinine-adjusted levels of OPs metabolites in the urine of Dutch pregnant women (N=100) from the Generation R study (Ye et al., 2008).

| Metabolites (nmol/g Cr) | Geometric Mean | Min. | Percentile | | | | | Max. |
|---|---|---|---|---|---|---|---|---|
| | | | 5th | 25th | 50th | 75th | 95th | |
| Total DMP | 240.0 | 51.3 | 74.3 | 163.1 | 264.3 | 379.2 | 655.9 | 1265.0 |
| Total DEP | 30.5 | 5.8 | 8.2 | 16.6 | 26.9 | 51.4 | 166.0 | 457.0 |
| **Total DAP** | **282.5** | **74.5** | **83.7** | **183.0** | **316.0** | **432.0** | **810.0** | **1552.0** |

*Calculation of IQ loss*

To calculate IQ loss, the Dutch population was divided in exposure groups based upon the typical distribution of measured exposure levels. For PBDEs, loss of cognition was only calculated for the highest 5% of the exposed population, the >P95 group. Only for this group there is evidence from the study by Chen et al. (2014) that Dutch PBDE exposure levels are situated within the range of the (sub-linear) effect curve of the ERR for IQ loss. Although this study provided no indication of a clear cut-off point for loss of cognition, the ERR was defined for levels above 3 ng/g lipid BDE-47. Therefore, in our study we took this value as a practical cut-off level for PBDE-associated loss of IQ points. We decided not to extrapolate the function described by Chen and co-workers below this 3 ng BDE-47/g lipid. Consequently, we calculated loss of IQ in the 95 percentile group based on the difference with this cut-off level of 3 ng BDE-47/g lipid and the geometric mean value of P95 and the maximum concentration measured in maternal serum.

For OP metabolite levels in maternal urine the situation was different as the Dutch levels were on average higher than those observed in the US. Therefore, IQ loss was calculated for the groups P50-P75, P75-95 and >P95 to max value. The difference between the median exposure level from the CHAMACOS cohort and geometric mean level between e.g. P75 and P95 levels were used to calculate the loss of IQ points as determined by Bouchard et al. (2011). Hence, we took the median US exposure level as a practical cut-off level for loss of cognition. Again, for the highest exposure group the difference between the median level and the geometric mean of the P95 value and maximum reported value of OP metabolites was used to calculate loss of IQ points.

For PBDEs as well as OPs we also used the upper and lower 95% Confidence Intervals (95% C.I.) of the ERRs published. This approach provided some indication of the uncertainties surrounding our estimations in IQ loss. All values were log10 transformed for compatibility with the selected ERRs from the US. We realize that from a mathematical point of view our approach is rather simple. However, it should be recognized that our calculations should only be used as an indication for the indirect costs for the Dutch society and be considered as order of magnitude estimates.

In 2013, 171 341 newborns were registered in the Netherlands (CBS, 2014). For each percentile group, the amount of newborns was calculated and multiplied by the estimate of IQ loss per newborn baby to calculate a total IQ loss per exposure group. It was assumed that effects on FSIQ at age 4-9 are permanent, consistent with permanent FSIQ effects due to methylmercury exposure (Debes, Budtz-Jørgensen, Weihe, White, & Grandjean, 2006).

*Economic valuation of lost IQ points*

The US EPA  adopted measures for calculation of socio-economic loss due to loss of IQ. A generic value of 2% loss in lifetime earnings for every IQ point is used (US EPA, 1997). This value consists of a direct effect (IQ on wage) of 0.5%, combined with two indirect effects (1.0% for less schooling and 0.477% for reduced labor force participation) (Ashenfelter & Ham, 1979; Krupnick et al., 1989; Needleman, Schell, Bellinger, Leviton, & Allred, 1990).

No estimate was available for the expected lifetime earnings of newborns in the Netherlands. The youngest age group for which such an estimate of expected average nominal lifetime labour income per capita is available, is for the age group 15-24 year olds. For this group, the Statistics Netherlands (CBS) derived an experimental value of € 1 037 000 (Rensman, 2013). However, due to the high amount of uncertainties, this value was considered unsuitable for calculations. Therefore, the generic value of average nominal lifetime labour income per capita of € 606 000 for all individuals in 2009 was used (Rensman, 2013). Considering the 2% loss of lifetime earnings, one IQ point was given an economic value of € 12 120.

## Results

*PBDE, loss of cognition and socio-economic costs*

For PBDEs, application of the ERR to the defined reference levels for the 5% highest exposure group (>P95) in the Netherlands, resulted in a loss of 1.0 IQ point per newborn baby (table 5). Real IQ loss per baby is most likely in the range of 0.0 – 1.9 lost IQ points, as is demonstrated by the 95% C.I. In total, it is calculated that on average over 8000 IQ points are lost per year of exposure in this group only. As a results, the total cost for these lost IQ point are estimated around € 100 million per year of exposure, with a 95% C.I. of € 2 million - € 196 million (table 5).

**Table 5.** Lost IQ points and associated socio-economic cost per year of PBDE exposure for the highest exposure group (>P95) of PBDE in the Netherlands. Calculations are based on the ERR from the HOME-study cohort (Chen et al., 2014)

| Exposure group | BDE-47 reference level (ng/g lipid) | IQ loss per newborn (95% C.I.) | Amount of new-borns | IQ loss per exposure group (95% C.I.) | Socio-economic cost (95% C.I.) (million € / year of exposure) |
|---|---|---|---|---|---|
| **>P95** | 4.91 | -0.96<br>(-1.88; -0.02) | 8567 | -8252<br>(-16 136; -183) | -100<br>(-196; -2) |

*OPs, loss of cognition and socio-economic costs*

Next, the loss of IQ points and related socio-economic cost were calculated for exposure to OPs, based on the ERR defined by Bouchard et al. (2011), and applied to defined reference levels of three different exposure groups (P50-P75, P75-P95 and >P95). Results are shown in table 6. Application of the ERR to Dutch exposure values resulted in a loss 5.1 IQ points for newborn babies in the highest 5% exposure group. 95% C.I. of these calculations show that the IQ loss for newborns in this group is most likely between a loss of 2.0 – 8.2 IQ points. Average total losses for all exposure groups combined are predicted of almost 220 000 IQ points per year of exposure. This equals to a total cost of € 2.7 billion (95% C.I. € 1.1 – 4.4 billion loss) per year of exposure.

**Table 6.** Lost IQ points and associated socio-economic cost per year of OPs exposure for three exposure groups in the Netherlands. Calculations are based on the ERR from the CHAMACOS –study cohort (Bouchard et al., 2011)

| Exposure group | Total DAP reference level (nmol/L) | IQ loss per newborn (95% C.I.) | Amount of new-borns | IQ loss per exposure group (95% C.I.) | Socio-economic cost (95% C.I.) (million € / year of exposure) |
|---|---|---|---|---|---|
| **P50-P75** | 272 | -1.69<br>(-2.72; -0.66) | 42 835 | -72 222<br>(-116 070; -28 373) | -875<br>(-1407; -344) |
| **P75-P95** | 494 | -3.14<br>(-5.04; -1.23) | 34 268 | -107 466<br>(-172 713; -42 219) | -1303<br>(-2093; -512) |
| **>P95** | 1116 | -5.12<br>(-8.23; -2.01) | 8567 | -43 856<br>(-70 483; -17229) | -532<br>(-854; -209) |
| **Total** | | | | **-223 455<br>(-359 266; -87 821)** | **-2709<br>(-4354; -1064)** |

## Discussion

*High socio-economic impacts are likely*

In this study it is demonstrated that the Dutch society bears high (indirect) costs caused by PBDE and OPs exposure and associated IQ loss. Socio-economic losses for PBDEs, are estimated at € 100 million (95% C.I. € 2 to 196 million loss) per year of exposure. Parallel to PBDEs, it is estimated that OPs are responsible for an even more dramatic socio-economic loss, of around € 2.7 billion (95% C.I. € 4.4 to 1.1 billion loss) per year of exposure. For OPs, we performed additional calculations of IQ loss based on the ERR defined by Engel (Engel et al., 2011). It was demonstrated that the application of various ERRs from different longitudal cohort studies provide outcomes of lost IQ points and related costs in the same order of magnitude. The fact that the results from more than one study point towards the same estimate of socio-economic costs does provide additional confidence in our estimations. For PBDEs, only one ERR could be applied to the Dutch situation due to exposure data limitations. However, two other ERRs from the literature indicate a similar relationship in IQ loss for PBDEs after prenatal exposure. The broad 95% C.I.s indicate that our estimations for both groups of compounds should not be taken too exact, but merely indicate the high the socio-economic impact that could be present.

*Estimated socio-economic costs likely represent only the "tip of the iceberg"*

In our present study, the scope was limited to PBDEs and OPs and IQ loss due to prenatal exposure. Another group of EDCs that are related to loss of cognition are the phthalates (Factor-Litvak et al., 2014). Since the published Dutch exposure values (Ye et al., 2008) are similar to the levels for which phthalates-related IQ loss was defined in the US (Factor-Litvak et al., 2014) the overall EDC-attributed IQ loss is maybe even higher than calculated in our present study. Furthermore, in our study no additional (direct) costs associated with intellectual disability (IQ < 70) were included. For PBDEs, no significant association between maternal PBDE exposure and child FSIQ <85 at age 5 years was found (Chen et al., 2014). In the cohort studies including OPs an increase in the amount of intellectual disabled children was not mentioned.

In our study we estimated that OP-related IQ loss and socio-economic impacts are over a billion € annually. This may very well represent a conservative value, as the median exposure level in the US cohort was used as a starting point for IQ loss. This was a pragmatic choice from our side, as no "safe concentration" has been published and the exposure of the US population could differ substantially from that of the Dutch population. Noticeable, the IQ loss in the US cohorts was already reported at lower levels than the cut-off levels we used, making it plausible that higher rates of IQ loss and socio-economic costs may be expected within the Dutch population.

In addition, our calculations were limited to an impact on IQ loss only. Other neurocognitive and neurobehavioral disorders, such as attention deficits/ADHD and autism spectrum disorders (ASD), were not included. Importantly, there are indications that such relationships may exist for PBDEs, e.g. attention deficits/ADHD (Eskenazi et al., 2013; Gascon et al., 2011; Herbstman et al., 2010). Comparable observations have been made for OPs and attention deficits/ADHD (Bouchard, Bellinger, Wright, & Weisskopf, 2010), OPs and autism (Eskenazi et al., 2007; Roberts et al., 2007), phthalates and attention deficits/ADHD(Marks et al., 2010), and phthalates and autism

(Miodovnik et al., 2011). If these factors could have been incorporated in our study, the, socio-economic (in)direct costs can expected to be much higher. As a result of these limitations in our study we consider the estimated socio-economic costs a significant underestimation.

*Realistic exposure levels for the Netherlands*

A strength of the present study is the fact that only Dutch exposure values have been used to calculate the socio-economic impacts. Since these levels were only coming from one study for each group of compounds, levels were also compared with other European studies.

For PBDEs, somewhat higher levels in pregnant women, but yet in a similar range, have been reported in a number of West-European studies. In 2011, PBDEs were analyzed in the serum of 98 pregnant women in Denmark with median concentrations of BDE-47 was 3.4 ng BDE-47/g lipid (min < 1.7; max 10) (Vorkamp et al., 2014), which is higher than the Dutch exposure values. Interestingly, an earlier study from Denmark reported a median BDE-47 value of 0.4 ng/g lipid (min <0.01; max 7.9) among 51 pregnant women (Frederiksen et al., 2010). In France, a median of 2.8 ng/g lipid BDE-47 was found (min 0.6; max 4.8) (Antignac et al., 2009). In Spain, a median BDE-47 of 2.4 (min 0.3; max 9.0) ng/g lipid and 2.6 (min 0.5; max 22) ng/g lipid was found in pregnant women living near Madrid (Gomara et al., 2007).

For OPs, fewer studies with European exposure levels exist compared to PBDEs. In a Norwegian Mother and Child Cohort study total DAP values were found to be lower than in the Dutch Generation R study, with an unadjusted geometric mean of 24.2 ug/L (*c.f.* 37.08 ug/L in the Netherlands) (Ye et al., 2009). These two studies are the only European studies measuring OPs in pregnant women. Other studies mostly concern exposure studies in occupational settings, and outside Europe. Only one other European study reported OPs metabolites in a non-occupational setting. In Greece OPs metabolites in urine were compared between 77 agricultural pesticide sprayers, 75 rural residents not involved in pesticide spraying and 112 urban residents. Results were shown as creatinine-adjusted (Koureas et al., 2014). When compared, the Dutch pregnant women had relatively high levels of DAP compared to other European states and the US (Bouchard et al., 2011; Engel et al., 2011) and even higher compared to the group of pesticide sprayers in Greece.

*Temporary trends of PBDE in serum difficult to indicate*

The costs calculated in this study are the annual socio-economic costs of PBDE exposure. These costs are recurring every year if exposure levels do not change. Our calculations were based on the only recent published ERRs and Dutch exposure levels. However, it is important to realize that these ERRs have been derived from sampling programs between 1998 and 2006 for OPs as well as PBDEs. Thus, the exposure levels used are approximately 10 to 15 years old and may not necessarily reflect the present situation. However, more recent appropriate studies for the Netherlands are lacking due to limited investments of the Dutch government in this field. PBDEs are relatively stable compounds with total-body half-lives between 2-12 years (Geyer et al., 2004), but OPs have a rapid renal elimination time, and metabolites are mostly excreted within 24 hours (Huen et al., 2012). Therefore, especially the exposure values for OPs could have changed substantially, but supporting Dutch data are fully lacking.

For PBDEs, it seems that median European exposure levels increased at least up to 2000, but the trend after this is difficult to obtain from literature (Darnerud et al., 2015; Thomsen et al., 2002; Thomsen, Liane, & Becher, 2007; Wiesmüller et al., 2007).
With respect to Dutch levels, somewhat higher levels of BDE-47 have been reported in adolescents compared to pregnant women but are generally in the same order of magnitude (Fromme et al., 2009; Fromme et al., 2015; Kicinski et al., 2012; Leijs et al., 2008). The difference in levels in pregnant women is probably due to added childhood exposure. In the US it was observed that younger age groups generally have higher PBDE serum levels compared to older people (Eskenazi et al., 2013; Rawn et al., 2014).

*The effects of OPs on cognitive functioning has not been studied in EU birth cohorts.*
The ERRs used in our calculations have been derived from US birth cohorts only. The use of these US data may introduce uncertainties with respect to the applicability to the Dutch population, for instance due to differences in genetics, food basket, and lifestyle. Unfortunately, no European birth cohorts have studied possible relationships between prenatal OP exposure and neurodevelopment, in spite of the fact that European levels of OP metabolites in urine are higher compared to the US (Spaan et al., 2014; Ye et al., 2009). This lack of information is a clear shortcoming with respect to human risk assessment, especially for the Netherlands OPs where prenatal levels are relatively high. Due to this lack of important information we had to assume that these ERRs from the US are also applicable for the Dutch situation. Another factor of concern may be to which extent single urinary DAP measurements do reflect chronic exposure to OPs during pregnancy, because of the short half-life and the intermittent nature of OPs exposure (Spaan et al., 2014). In future studies, repeated measurements will clearly increase the reliability in background exposure assessment and possible negative associations with cognitive development in children.

*Subtle effects from PBDE exposure in the EU*
For PBDEs, a few EU studies towards pre- and postnatal PBDE exposure and cognitive functioning have been performed. Despite the fact that negative effects on FSIQ have so far not been found in EU cohort studies, several more subtle negative and positive effects on cognitive, motor function and neurobehavioral domains have been described (Gascon et al., 2011; Kicinski et al., 2012; Roze et al., 2009). European studies did not find significant effects of PBDE exposure on IQ, however this could be a result of lower sample sizes compared to US cohorts, and/or difficulties in quantification due to lower EU levels in humans. However, these lower European exposure levels are still correlating to subtle cognitive effects, as well as effects on the thyroid hormone homeostasis (Kicinski et al., 2012; Roze et al., 2009). Thus, an *a priori* statement that the lower EU (Dutch) PBDE levels should not cause a neurodevelopmental effect after perinatal exposure appears to be premature and preliminary data direct towards the opposite.

*For ERRs the use of genetically susceptible populations has preference above whole populations.*
Different subpopulations could pose different susceptibilities to environmental contaminants. This seems the case for OPs-induced neurodevelopmental effects (Engel et al., 2011; Eskenazi et al., 2014). Within the both US cohorts used in our study, it was noted that susceptibility to OPs

exposure is affected by genotype. The New York birth cohort study demonstrated that mothers with PON1 Q192 R Q/Q genotype had a lower catalytic activity of PON1, the key enzyme for OP metabolism, This resulted in larger decrements of IQ compared to the other genotypes (Engel et al., 2011). Similar observations have been published from the CHAMACOS cohort, that underline the importance of the arylesterase (ARYase) enzyme during pregnancy (Eskenazi et al., 2014). Thus, future studies should focus on these sensitive genotypes to refine sensitive subpopulations better.

*Comparison of results to earlier reports on EDC-related costs*

Studies on the contribution of environmental pollutants to morbidity, mortality, and e.g. costs of pediatric diseases have been done before. In variable, these studies have estimated high societal costs as was shown for the US and Canada (Landrigan, Schechter, Lipton, Fahs, & Schwartz, 2002; Muir & Zegarac, 2001). Moreover, Full-Scale IQ points lost among U.S. children, 0–5 years of age, were estimated for chemicals (methylmercury, organophosphate pesticides, lead) and a variety of adverse health effects, e.g. preterm birth, traumatic brain injury, brain tumors, and congenital heart disease (Bellinger, 2012). The results of our study are best to be compared with those of Trasande and co-workers (Trasande et al., 2015). Within this group of scientist, Bellanger and co-workers (2015), also calculated IQ loss and associated societal costs for PBDE and OPs in the EU. If these results are used to predict the socio-economic costs for the Netherlands based on the number of inhabitants in our country *versus* those in the EU, this would amount in € 280 million (sensitivity analysis € 48 – 650 million) annually. In this case our calculation of € 100 million socio-economic costs for PBDEs are well within this range. Similarly, costs were calculated of the effects of OPs on IQ in the EU (Bellanger et al., 2015). If we again convert this to the Dutch situation, based on number of inhabitants, the socio-economic costs would be € 4.17 billion (sensitivity analysis € 1.36 – 5.5 billion) annually. Our estimation of € 2.7 billion costs for OPs is well comparable again.

*Discussion exists on the economic value of IQ points.*

Obviously, the societal costs of the loss of one IQ point largely influences socio-economic impact due to EDC exposure. In our present study, 2% loss in lifetime earnings for every IQ point has been used (US EPA, 1997), which corresponds to € 12 120 for the Netherlands. The US EPA also described a (newer) approach in which the loss of an IQ point is equivalent to a reduction in earnings of 1.93% for men and 3.22% for women (Salkever, 1995). To our opinion this approach has more uncertainties, as the labour participation of women varies among years and between countries. Furthermore, child sex is reported not to have an interaction with PBDE levels and test scores (Chen et al., 2014; Eskenazi et al., 2013). Therefore, we decided to use the generic value of 2% for all sexes.

Considering differences in income and labour force participation between the US and Europe, it would be best to use European studies to estimate the effect of IQ on income. However, these are not available. In a review performed by European Chemicals Agency (ECHA) it was concluded that economic loss due to IQ would be considerably lower compared to the US, around 1% (0.3-1.5%) of lifetime earnings per IQ point (ECHA, 2014). This conclusion was based on more recent studies

(Heckman, Stixrud, & Urzua, 2006; Zax & Rees, 2002) than those of the US EPA. However the effect on increased labour force participation (+0,5%) and stronger effects for females (+1%) were neglected in this approach. As a result we retained the value of 2% to calculate economic losses. The ECHA concluded that the benefit (cost) per IQ-point gained (lost) is around € 8000, with an uncertainty range of € 2400 – 25 000. Our calculated value of € 12 120 for the Netherlands is well within this range.

*Perspectives for the future and recommendations*

It is unlikely that economic losses due to IQ loss associated with PBDE exposure will significantly decrease in the near future. Although already banned for commercial use for some years, these PBDEs are persistent, with long half-lives in the environment and humans (Geyer et al., 2004; Thuresson et al., 2006). One recommendation to women and couples who want to become pregnant, could be to keep their home vacuum-cleaned to reduce ingestion of dust. This is also important for households were young children crawl on the floor. Postnatal exposure to PBDEs has also been associated with decrements in IQ and other behavioral outcomes (Eskenazi et al., 2013). However, this measure could only reduce exposure to PBDEs to a certain extent as these compounds are also present in the human food chain.

Many OPs, but not all, are banned in the EU and the Netherlands. For instance, the OPs insecticides chlorpyrifos and dimethoathe are not banned in the EU although current Dutch use is low (Statistics Netherlands (CBS), 2014). In contrast to PBDEs, OPs are rapidly metabolized to one or more DAP metabolites in the body. Due to their short half-life, OPs are almost completely excreted via the urine within 24h (Huen et al., 2012). In view of this rapid elimination, women who are or want to become pregnant can eliminate OPs from their body efficiently within a couple of days, if the exposure situation ceases.

In general, urinary OPs metabolite levels represent exposure to parent OP pesticides and their metabolites either from dietary intake or direct exposure to pesticides (Barr & Needham, 2002). In urban situations, it is assumed that DAP levels in urine are to a large extent the result of dietary intake via consumption of fruits and vegetables with OP pesticide residues (Spaan et al., 2014). In the EU maximum levels of OPs residues on food are implemented, but monitoring campaigns revealed that maximum residue levels on food are still frequently exceeded. These situations seem to occur more often on non-EU fruits and vegetables (EFSA, 2015; Nederlandse Voedsel- en Warenautoriteit (NVWA), 2014).

The observed OPs-associated IQ loss can at least partly be mitigated by pregnant women through reducing the chance of exposure. Thorough washing and peeling of fruits or vegetables, and avoid fruits and vegetables from certain (mostly non-EU) countries during pregnancy may help in this respect. However, both suggestions are based on a precautionary principle, as it will usually be unknown if a specific food product has residue levels exceeding the maximum. In general, it can be assumed that fruit and vegetables from European origin will not contain OP levels that exceed maximum residue level and are therefore safe to consume by pregnant women.

Besides dietary intake of pesticides residues, exposure of OPs could also be a result from flea control measures of pets. A study in the US by the Natural Resource Defense Council (NRDC)

showed that high levels of pesticide residues can remain on the fur of a dog or cat for weeks after a flea collar is put on (Rotkin-Ellman & Solomon, 2009). Whether this is also the case with flea collars in the EU is unknown. Based on the results presented in our study, it is recommended that households with pregnant women should refrain from the use flea control measures that contain OPs.

## Conclusions

Our study suggests that, based upon Dutch exposure levels of PBDE and OPs from the beginning of the 21$^{st}$ century, part of the general population is exposed to levels which are associated with loss of IQ in their children. These effects are most significant for OP-related loss of IQ in early childhood. Our best estimates of PBDE- and OP-related IQ loss leads to socio-economic (indirect) costs of respectively € 100 million and € 2.7 billion anually. With these results in mind, it is suggested to reduce and prevent exposure to EDCs more to protect future generations and bring down unnecessary socio-economic costs.

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