ENVIRONMENTAL CONTAMINANTS AND LUNG FUNCTION – THE MISSING LINK

Gavin W. ten Tusscher[1], Marike M. Leijs[6, 2, 3] ,Wim M.C. van Aalderen[3], Kees Olie[2], Pim de Voogt[2,5], Juliette Legler [7], Janna G. Koppe[4*]

[1]Department of Paediatrics and Neonatology, Westfriesgasthuis, Maelsonstraat 3, 1624 NP Hoorn, The Netherlands;[2]IBED/ESS,University of Amsterdam,The Netherlands;[3] Department of Paediatric Respiratory Medicine and Allergy, Emma Children's Hospital Academic Medical Centre, Amsterdam, The Netherlands; [4]Ecobaby Foundation, Loenersloot, The Netherlands;[5] KWR Watercycle Research Institute, POBox 1072, 3430 BB Nieuwegein, Netherlands,[6] University Hospital Aachen, Department of Dermatology, 52074 Aachen Germany.[7]Institute for Environmental Studies VU University Amsterdam, De Boelelaan 1085,1081HV Amsterdam, The Netherlands.

*Janna Koppe is presenter
Gavin ten Tusscher and Marike Leijs share the first authorship.

Introduction

The high incidence of respiratory disease throughout the (Western) world is not yet fully understood. While genetic factors certainly play a role, they do not provide sufficient explanation. Over the last decades it has been commonly accepted that environmental pollutants are a cofactor in respiratory disease. Ever since, environmental factors have received more attention.

Are environmental pollutants the missing link? In this manuscript we consider some widespread specific environmental contaminants like dioxins, PCBs and PBDEs in relation to lung function.

Polychlorinated dioxins and furans (henceforth jointly referred to as dioxins) belong to the group of most toxic substances known, and have been associated with malignancy, congenital malformations, immunosuppression and respiratory disorders [1-4].

Another group of compounds, the polybrominated diphenylethers (PBDEs) have been widely used over the last few decades as flame retardants in various materials such as electronic equipment, plastics, carpet liners and textiles. Humans are exposed to PBDEs mainly by ingestion and by inhalation. Numerous recent publications have shown the presence of PBDEs in dust, also in homes [5].

In an earlier follow-up of our cohort a negative association was found between de prenatal and lactational dioxin exposure and the FEV1/FVC ratio [4], showing that perinatal exposure to dioxins and related compounds may have consequences spanning many years. Moreover, in both animals and humans, the respiratory system is a target of dioxin-toxicity [4,6,7].

In our longitudinal cohort study of the development of children with known perinatal dioxin exposure, now nearing the end of its second decade, we therefore assessed the lung function of the study participants, using spirometry and a detailed medical history.

Materials and methods

Study population: This study is part of a longitudinal cohort study of currently 14-19 year old children, studied during their neonatal (n=60) [8,9], toddler (n=60) [10] and pre-pubertal period (n=41) [11]. All 33 children (18 girls and 15 boys) participating in the current follow-up were born in the Amsterdam/Zaandam region of the Netherlands. Dioxin exposure was determined in the perinatal period in breast milk.

Medical examination: A medical history was taken by one and the same physician using a questionnaire which included a history of asthma and smoking habits. The questionnaire also included general questions regarding the pubertal development and other reproductive features and general information such as current school and

electives/vocation (e.g. agricultural with possible pesticide exposure) and to assess unusual food intake. Lung function measurements were performed using the Masterscreen PFT plus bodybox (Jaeger Viasys, Germany). Lung function parameters that were obtained and evaluated were spirometric values (VC MAX, FEV 1, FEV1/VC MAX, PEF, FEF 50), diffusion measurements (TLCO SB, VA, VIN), and measurements in the body box (VC MAX, TLC, RV, RV%TLC, FRC). ERS principles were adhered to (European Respiratory Society, 1993).

Laboratory analyses: Perinatal PCDD/F levels and current serum levels of PCDD/Fs, PCBs and PBDEs were determined in an uncontaminated laboratory at the Institute for Biodiversity and Ecosystem Dynamics of the University of Amsterdam. Concentrations of the 19 most toxic dioxin congeners (seven PCDDs and twelve PCDFs) and the concentration of 3 dioxin-like PCBs (77, 126, 169) and 8 PBDEs (28, 47, 85, 99, 100, 153, 154 and183) were measured. The concentrations of dioxin and dioxin-like PCB (dl-PCB) congeners were expressed in toxic equivalents (TEQ) ng/kg fat in serum.

Statistical analyses: For statistical analyses Spearman's rho correlation was calculated using the software package SPSS®. Zapletal normal values for lung function measurements were used [12].

Results and discussion

Prenatal and lactational dioxin exposure in relation to current lung function: A negative trend was found between prenatal dioxin exposure and FEV1 ($p=0.069$) for the girls ($n=18$). For the complete cohort no significant associations were found. In contrast to our earlier findings, there was no longer a relation seen between FEV1/FVC and prenatal nor with lactational dioxin exposure.

Current serum dioxin, dl-PCBs and total TEQ in relation to current lung function: A positive relationship was seen between current serum dioxin levels and FEV1 ($p=0.038$), and TLCO ($p=0.026$) in girls. No associations were seen in the boys. For the dl-PCBs no relation was found with lung function, similar to a recent German study [13].

In contrast to the prepubertal study, no relation between perinatal dioxin exposure and lung function was seen during the puberty follow-up in the whole group. This could possibly point to an improvement in the lung function deficit following further clearance of the high perinatal exposure. The half-life of dioxins are estimated at 7-12 years, but may be shorter [14]. The cohort was aged 14-19 years at the current follow-up. The prenatal and lactational dioxin and PCB exposures are around 26 times higher than later, when the intake of animal fats and human breast milk is far lower [15]. This is also seen in the measured current serum dioxin and PCB exposures [16]. Animal studies have shown common environmental contaminant exposure to result in smaller numbers of alveoli and less branching of the pulmonary tree [17]. The number of alveoli and branching of the pulmonary tree do not increase after infancy [18,19]. The limited subjects in the current follow-up may lead to wrong conclusions.

Various major accidents, resulting in large populations being exposed to high concentrations of dioxins, PCBs and furans have occurred. PCB, dioxin and furan exposure following rice oil contamination in Japan, in 1968, caused chronic bronchitis in 40% of the exposed and persistent suboptimal lung function [20]. A similar incident on Taiwan Island led to 25% of the highly exposed babies dying within four years after birth as a result of respiratory disorders. Respiratory distress and pneumonia during the first six months of life were common [21,22]. The explosion at an Italian chemical plant led to high dioxin exposure, causing an increased mortality risk for respiratory disease, mainly chronic obstructive pulmonary diseases (COPD). However, it must be borne in mind that, contrary to our study, these accidents were the result of an acute toxic effect with a high exposure level and not of a developmental effect.

Current serum BDEs in relation to lung function: A significant negative relation was found with sum BDE and FEF 50 ($p=0.016$) (see figure 1). For BDE 100 and BDE-99 a significant negative relation was found with FEV1/VCMAX ($p=0.031$ and $p=0.049$). This follow-up study suggests that brominated diphenyl ethers negatively affect lung function in relation to increasing BDE exposure in the teenagers.

The decrease in lung function in relation to increasing prenatal and lactational dioxin exposure as presented in childhood is no longer visible in adolescence[4]. This observation suggests that at least a portion of the increased incidence of asthma throughout the Western World over the past decades may be the result of increasing BDE exposure. To our knowledge we are the first to link serum BDE levels to lung function deficits. We measured

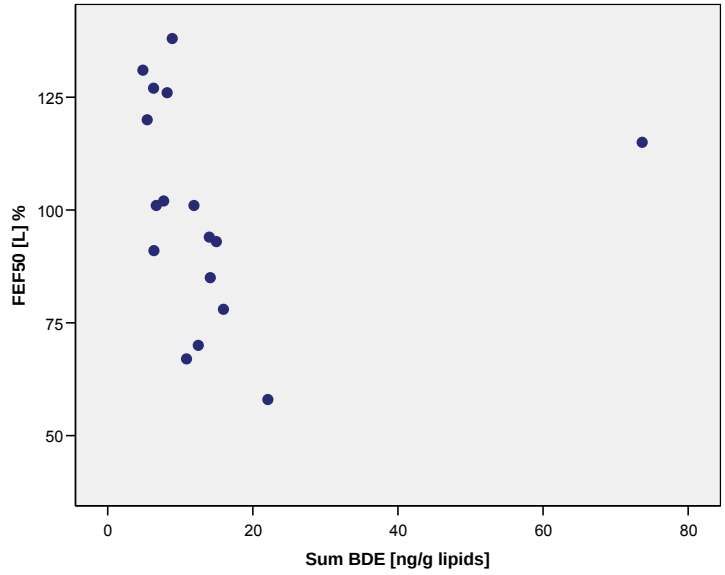
current BDE levels. The perinatal levels are not known. It is alarming to find a relation between BDEs and lung function. Polybrominated diphenyl ethers are very commonly used substances worldwide. It is then not surprising that human levels have increased over the last years [23]. Furthermore, indoor dust contains far higher concentrations than outdoor air [24]. Recent studies have linked BDE exposures and endocrine disruption and neurotoxicity [25-29]. Further scientific evidence of adverse health effects is still wanting or unexplored.

The lung function outcomes would seem to plead for an increased obstructive component in the respiratory system, as a result of the BDE exposure. An increase in an obstructive component would suggest an increase in asthmatic complaints. It is then interesting to note that the enormous increase in the incidence of asthma during the 80's and 90's of the previous century, were at a time when the use of (and exposure to) BDE's rapidly increased worldwide, especially in the Western World. This prompts us to hypothesise that at least a portion of the increased incidence of asthma throughout the Western World is the result of increasing BDE exposure. However, the size of our current cohort limits us in evaluating asthma and BDE separately.

However, it must be borne in mind that obstructive lung disease encompasses more than asthma. In our study, obstructive processes may result from a decrease in airway wall integrity, or reduced lung elasticity. A developmental effect or direct toxic effect could then probably be the aetiological factor. Further research is needed to elucidate the findings presented in this manuscript.

Conclusion: While the in childhood present decrease in lung function in relation to increasing prenatal and lactational dioxin exposure is no longer visible in adolescence, a decrease in lung function is now seen in relation to increasing BDE exposure in the teenagers. This is a novel finding and certainly warrants further research.

Figure 1: A significant negative relationship between sum BDE and FEF 50 (p=0.016)



Acknowledgements
The authors wish to thank the participants of the study, and their parents, for their cooperation; Dr. J. Oosting for his help with the statistics; and P. Serné, F. vd Wielen and J. Parsons of the laboratory of the Institute for Biodiversity and Ecosystem Dynamics for their help with the chemical measurements. We are indebted to dr.

Matthijs Westra paediatrician for his help to investigate the children in the Zaans Medical Centre “De Heel” Zaandam.
The study was supported by E.C.grant: OBELIX : 227391

References:

1. ten Tusscher GW, Koppe JG. (2004) Chemosphere;54(9):1329-36.
2. ten Tusscher GW, Stam GA, Koppe JG. (2000) Chemosphere;40(9-11):1263-70.
3. ten Tusscher GW, Steerenberg PA, van Loveren H, Vos JG, dem Borne AE, Westra M et al. (2003) Environ Health Perspect,111(12):1519-23.
4. ten Tusscher GW, de WJ, Roos CM, Griffioen RW, De Jongh FH, Westra M et al. (2001) Acta Paediatr: 90(11):1292-8.
5. Harrad S, Hunter S. (2006) Environ Sci Technol 1;40(15):4548-53.
6. Pesatori AC, Zocchetti C, Guercilena S, Consonni D, Turrini D, Bertazzi PA. (1998) Occup Environ Med;55(2):126-31.
7. World Health Organization (WHO/IPCS).(1989). Report No.: EHC 88.
8. Pluim HJ, Koppe JG, Olie K, Vd Slikke JW, Kok JH, Vulsma T et al. (1992) Lancet ;339(8804):1303.
9. Pluim HJ (2003). pre- and postnatal exposure in the human newborn: Thesis University of Amsterdam.
10. Ilsen A, Briet JM, Koppe JG, Pluim HJ, Oosting J. Chemosphere 1996;33(7):1317-26.
11. ten Tusscher GW (2002). Later childhood effects of perinatal exposure to background levels of dioxins in the Netherlands. Thesis University of Amsterdam.
12. Zapletal A, Samanek M, Paul T. (1987) Lung function in children and adolescents. Book: ISBN 978-3-8055-4495-5
13. Link B, Gabrio T, Zollner I, Piechotowski I, Kouros B. (2007) Int J Hyg Environ Health;210(3-4):351-5.
14. Research Triangle Institute. Toxicological profile for chlorinated dibenzo-p-dioxins. (1997) Update ed. Atlanta: Agency for Toxic Substances and Disease Registry.
15. Patandin S, Dagnelie PC, Mulder PG, Op de CE, van d, V, Weisglas-Kuperus N et al. (1999) Environ Health Perspect 1999;107(1):45-51.
16. Leijs MM, Teunenbroek T, Olie K, Koppe JG, Tusscher GW, Aalderen WM et al. (2008) Chemosphere;73(2):176-81.
17. Avdalovic M, Putney L, Tyler N, Finkbeiner W, Pinkerton K, Hyde D. (2009)Toxicol Pathol 2009;37(2):256-63.
18. Beech DJ, Sibbons PD, Howard CV, van Velzen D. (2000) Early Hum Dev.59(3):193-200.
19. Beech DJ, Howard CV, Reed MG, Sibbons PD, van Velzen D. (2000) J Microsc.197(Pt 1):36-45.
20. Fukuoka. Yusho. (1996) Kyushu University Press.
21. Rogan WJ, Gladen BC, Hung KL, Koong SL, Shih LY, Taylor JS et al. (1988) Science. 241(4863):334-6.
22. Chen HS., Yeng Y. (1981) Clin Med. 7:96-100.
23. Zuurbier M, Leijs M, Schoeters G, ten TG, Koppe JG. (2006) Acta Paediatr Suppl. 95(453):65-70.
24. Harrad S, Hazrati S, Ibarra C. Environ Sci Technol ;40(15):4633-8.
25. Roze E, Meijer L, Bakker A, van Braeckel KNJA, Sauer JJ, Bos AF. (2009) Environ Health Perspect
26. Viberg H. (2009) Int J Dev Neurosci,27(5):423-9.
27. Talsness CE, Kuriyama SN, Sterner-Kock A, Schnitker P, Grande SW, Shakibaei M et al. (2008) Environ Health Perspect. 116(3):308-14.
28. Viberg H. (2009) Toxicol Sci.109(2):306-11
29. Leijs M.M., Koppe J.G., Olie K., van Aalderen W.M.C., de Voogt P., ten Tusscher G.W. (2009) Environmental Science & Technology. 43 (20), 7946–7951.