Environment International 94 (2016) 399–407

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Perinatal exposure to dioxins and dioxin-like compounds and infant growth and body mass index at seven years: A pooled analysis of three European birth cohorts

Nina Iszatt [a], Hein Stigum [a], Eva Govarts [b], Lubica Palkovicova Murinova [c], Greet Schoeters [b,d,e], Tomas Trnovec [c], Juliette Legler [f,1], Cathrine Thomsen [g], Gudrun Koppen [b], Merete Eggesbø [a,*]

[a] Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway
[b] VITO, Unit of Environmental Risk and Health, Mol, Belgium
[c] Slovak Medical University, Faculty of Public Health, Department of Environmental Medicine, Bratislava, Slovakia
[d] University of Southern Denmark, Department of Environmental Medicine, Odense, Denmark
[e] University of Antwerp, Department of Biomedical Sciences, Antwerp, Belgium
[f] VU University Amsterdam, Institute for Environmental Studies, Amsterdam, The Netherlands
[g] Division of Environmental Medicine, Norwegian Institute of Public Health, Oslo, Norway

ARTICLE INFO

Article history:
Received 1 February 2016
Received in revised form 31 March 2016
Accepted 24 April 2016
Available online 14 June 2016

Keywords:
Dioxins
Dioxin-like PCBs
Birth cohorts
Infant growth
BMI
Obesity

ABSTRACT

Background: Dioxins and dioxin-like compounds are endocrine disrupting chemicals (EDCs). Experimental studies suggest perinatal exposure to EDCs results in later obesity. However, the few epidemiological investigations on dioxins are inconclusive. We investigated perinatal exposure to dioxins and dioxin-like compounds, infant growth and body mass index (BMI) in childhood.

Methods: We pooled data from 3 European birth cohorts (Belgian, Norwegian, Slovak) with exposure assessment in cord blood or breast milk. Two cohorts had dioxin-like toxicity assessed using dioxin-responsive chemical-activated luciferase expression (DR-CALUX) bioassay and one cohort had measured concentrations of dioxins, furans and dioxin-like polychlorinated biphenols with CALUX relative potency values applied. Growth was cohort- and sex-specific change in weight-for-age z-score between birth and 24 months (N = 367). BMI was calculated at around 7 years (median 7.17, interquartile range [IQR] 7.00–7.37 years, N = 251), and overweight defined according to international standards for children equivalent to adult BMI >25 kg/m^2 (Cole and Lobstein, 2012). We fitted multivariate models using generalized estimating equations, and tested effect modification by sex, breastfeeding and cohort. Results per 10 pg CALUX TEQ/g lipid increase in exposure.

Results: Dioxin exposure was highest in the Belgian and lowest in the Norwegian cohort; median (IQR) of the pooled sample 13 (12.0) pg CALUX TEQ/g lipid. Perinatal exposure to dioxins and dioxin-like compounds appeared associated with increased growth between 0 and 24 months (adjusted estimate for change in z-score: β = 0.07, 95% CI: −0.01, 0.14). At 7 years, dioxins exposure was associated with a statistically significant increase in BMI in girls (adjusted estimate for BMI units β = 0.49, 95% CI: 0.07, 0.91) but not in boys (β = −0.03, 95% CI: −0.55, 0.49) (*p*-interaction = 0.044). Furthermore, girls had a 54% (−6%, 151%) increased risk of overweight at 7 years (*p*-interaction = 0.023).

Conclusion: Perinatal exposure to dioxin and dioxin-like compounds was associated with increased early infant growth, and increased BMI in school age girls. Studies in larger sample sizes are required to confirm these sex-specific effects.

1. Introduction

Dioxins and dioxin-like compounds (DLCs) are among the most toxic pollutants known to science. This class of compounds includes dioxins or polychlorinated dibenzo-*p*-dioxins (PCDDs), of which 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) is the most toxic, polychlorinated dibenzofurans (PCDFs), as well as some polychlorinated biphenyls (PCBs) [hereafter "dioxins" refers to dioxins and DLCs]. Dioxins are largely unintentional by-products of various industrial processes, such as smelting and herbicide and pesticide manufacture. Although stricter legislation has curtailed environmental release of these pollutants, they are prevalent in the environment and likely to remain so for some time due to biomagnification, bioaccumulation and long half-

* Corresponding author at: Norwegian Institute of Public Health, P.O. Box 4404 Nydalen, N-0403 Oslo, Norway.
E-mail address: merete.eggesbo@fhi.no (M. Eggesbø).
[1] Current address: Brunel University London, Institute of Environment, Health and Societies, Uxbridge, UK.

http://dx.doi.org/10.1016/j.envint.2016.04.040
0160-4120/

lives. TCDD has a half-life of 7–8 years in humans (Kogevinas, 2001), while some other DLCs have half-lives of more than a decade (Milbrath et al., 2009). >90% of human exposure is through food (Djien Liem et al., 2000). Infants are then exposed to maternal blood concentrations *in utero* and through breast milk and food during infancy. During a short period of breastfeeding, they are exposed to concentrations that are 10–20 fold higher than the recommended exposure concentrations (Stigum et al., 2005).The biological mechanism of action of all these compounds is mediated via activation of the cellular protein aryl hydrocarbon receptor (AhR) (Birnbaum, 1994). The World Health Organisation has developed toxic equivalency factors (TEF) for DLCs relative to TCDD based on *in vivo* studies of DLCs which have a structural relationship to dioxins, bind to the AhR, and elicit AhR-mediated biochemical and toxic responses, allowing for risk assessment of DLCs as a complex mixture (Van den Berg et al., 2006).

Dioxins are primarily a health concern as human carcinogens (Baan et al., 2009), however, recent attention is on their endocrine disrupting properties, particularly at low exposures. Experimental studies suggest that, as a down-stream function of AhR activation, dioxins are endocrine disrupting chemicals (EDCs), including effects on thyroid function, insulin and growth (Kogevinas, 2001). The direction of the effect on growth is, however, not entirely clear. For example, *in vitro*, adipocyte differentiation was inhibited by TCDD (⩾0.1 nM) (Bastos Sales et al., 2013). In female adult mice fed a high fat diet, high doses but not low doses of TCDD induced obesity (Zhu et al., 2008). Few epidemiological studies have investigated perinatal exposure to dioxins and indicators of obesity, and the evidence is also inconclusive (Delvaux et al., 2014; Nishijo et al., 2012; Patandin et al., 1998; Su et al., 2010; Verhulst et al., 2009; Wohlfahrt-Veje et al., 2014). Previous studies were in smaller samples (Delvaux et al., 2014; Su et al., 2010; Verhulst et al., 2009), or only studied body mass index (BMI) and other fat measures during infancy (Nishijo et al., 2012; Patandin et al., 1998; Verhulst et al., 2009; Wohlfahrt-Veje et al., 2014) and not later in childhood.

We investigated the association between perinatal exposure to dioxins and infant growth and BMI in later childhood in three European birth cohorts.

2. Methods

2.1. Description of cohorts

Within the framework of the EU project OBELIX (Legler et al., 2011) a collaboration was established between 3 European birth cohorts: the Norwegian HUMIS study (Eggesbø et al., 2009, 2011), the Flemish FLEHS I study (Koppen et al., 2009) and the Slovak PCB cohort (Hertz-Picciotto et al., 2003). Table 1 contains cohorts' descriptions and references. The mother-child pairs were recruited in the period from 2002 until 2004 (PCB cohort N = 1137, FLEHS I, N = 1196) and until 2009 (HUMIS, N = 2606). Based on random sampling, exposure biomarkers for dioxins were measured in breast milk (HUMIS, N = 64 and PCB cohort, N = 208). In FLEHS I, dioxins were measured in cord serum based on availability of volume (N = 857). Only 152 of the FLEHS I newborns were in the subcohort intended for follow up, of which one twin was excluded, leaving 96 with dioxin biomarkers and infant growth data and 64 with BMI at 7 years. Some participants in PCB cohort were lost to follow up and therefore were missing growth or BMI at 7 years data, resulting in 207 with dioxin biomarkers and infant growth data and 160 with BMI at 7 years. All HUMIS children with dioxin biomarkers had infant growth data (N = 64) but weight and height data was available in a small sample at 7 years (N = 27) through linkage with the MoBa study (Magnus et al., 2006). The final pooled analyses had N = 367 for infant growth and N = 251 for BMI at 7 years (Table 1). Each study was approved by national ethical committees and mothers provided written informed consent prior to participation.

Table 1
Description of the birth cohorts with exposure biomarkers included in the present study[a].

Cohort	Setting location	Time period	Enrolment method	Exclusion criteria	Participation rate	Age weight/height data collection	Exposure assessment[b]		N in cohort	N with dioxin biomarkers	N in this study (2 years)	N in this study (7 years)	Source
							Biological matrix	Time of collection					
FLEHS I	Belgium (Flanders)	2002–2004	At delivery in maternities of 8 districts covering 20% of Flanders' area	Complications in delivery; Living <5 years in the area; Not Dutch reading	98%	0, 12, 18, 24, 30, 36 months	Cord plasma	At birth	1196	857	96	64	Koppen et al. (2009)
PCB cohort	Slovakia	2002–2004	At delivery in maternities of 2 districts, 1 with high PCB contamination (Michalovce), and another upwind and upstream of chemical facility with lower contamination (Svidnik).	Mothers with major illness; Severe congenital anomalies; Maternal age <18 years; Living <5 years in the area; Parity >4	60%	0, 6, 18, 48 months	Breast milk	Within day 4–5 after delivery	1134	208	207	160	Hertz-Picciotto et al. (2003)
HUMIS	Norway	2002–2009	Two-four weeks after birth during the routine health visit at home	Non-fluent in Norwegian	64%	Average 7 measures collected across 0, 6, 12, 24 months	Breast milk	Mixture of multiple samplings (Milk collected for eight consecutive days around 1 month after birth and)	2606	64	64	27	Eggesbø et al. (2009) & Eggesbø et al. (2011) supplements

[a] Adapted from Govarts et al. (2012). Reproduced with permission from *Environmental Health Perspectives*.
[b] Selection criteria for exposure assessment was availability of biological samples except for HUMIS (random selection in cohort, breastfeeding).