# Delayed initiation of breast development in girls with higher prenatal dioxin exposure

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*Introduction:*
Polychlorinated dibenzo-p-dioxin (PCDDs) and polychlorinated dibenzofurans (PCDFs), often grouped together as 'dioxins', are of the most dangerous toxic environmental contaminants. Dioxins and dioxin-like compounds are able to bind to the AhR- receptor. They are considered to alter puberty by behaving as anti-estrogens, decreasing levels of functional estrogen-receptors and by disruption of thyroid homeostasis, which is essential for normal body metabolism, growth, and development.
As part of a longitudinal cohort study, now in its second decade, we assessed pubertal development and growth in adolescents, in relation to perinatal and current dioxin (PCDD/F) exposure.

*Study population:*
In this study, average Dutch children exposed to background levels of dioxins were studied. The subjects, now aged 14-19 years, were previously assessed during their neonatal (n=60) (1), toddler (2) and pre-pubertal period (n=44) (3;4). All 32 children, consenting to the current follow-up study, were born in the Amsterdam/Zaandam region of The Netherlands.

*Methods:*
Pubertal development and growth were determined using the Tanner scale, physical examination and a questionnaire during an interview with the mother and the adolescent. Prenatal, lactational and current dioxin concentrations were determined using high resolution GC-MS (HP 5970 GC, Kratos Concept MS). For the current dioxin concentration, blood samples were obtained by vena puncture. TEQ values were based on the concentrations of the seventeen most toxic congeners (seven dioxins and ten dibenzofurans).

*Results:*
Preliminary results show a relation between initiation of breast development in girls (n=18) and their prenatal dioxin exposure (p=0.025) (see figure 1). After correction for BMI this relation was even more significant (p=0.016). The results show that current serum dioxin was not significant related with initiation of breast development.
Lactational exposure showed a tendency to correlate with breast development (p=0.097). After correction for BMI this relation was significant (p=0.045). The results show no relation between current breast stage for perinatal and current serum dioxin concentration.
Serum concentrations of lead, measured in the subjects' pre-pubertal period, had no influence on these outcomes.
Means and ranges are shown in table 1:

*Table 1: Means and ranges*

| | Mean | Lowest value | Highest value |
|---|---|---|---|
| Age at initiation breast development (years) | 12 | 10 | 14 |
| BMI (kg/m$^2$) | 20,97 | 17,39 | 30,86 |
| Current serum dioxin (TEQ) (ng/kg fat)[1] | 1,88 | 0.7100 | 4.55 |
| Prenatal dioxin exposure (TEQ) (ng/kg fat) | 32,64 | 9,05 | 59,84 |
| Postnatal (lactational) exposure (TEQ) (ng) | 75.4 | 4.34 | 279.7 |

[1] preliminary result

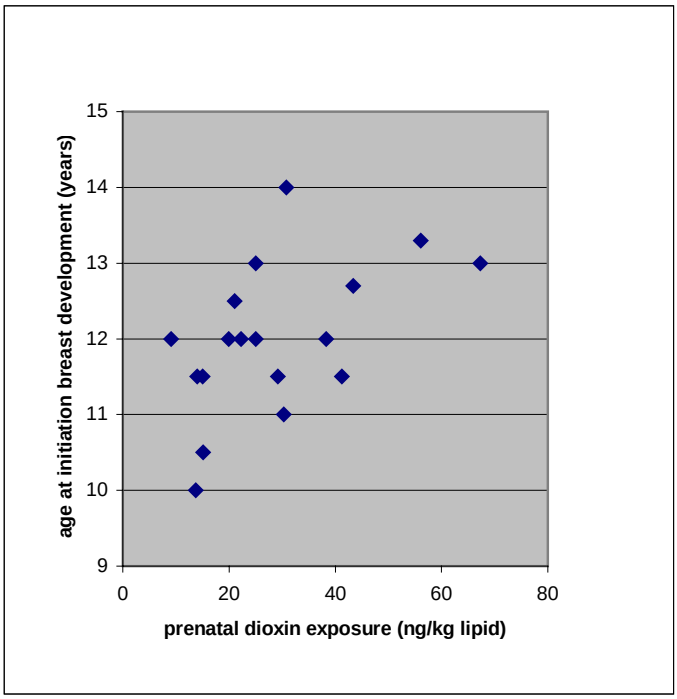


*Figure 1: Initiation of breast development and prenatal dioxin exposure in girls*

*Discussion and conclusions:*
Preliminary results indicate a correlation between prenatal and lactational dioxin exposure and retardation of initiation of breast development in our longitudinal Dutch dioxin study. Den Hond's study showed a retardation in breast development with current serum dioxin concentrations (5).

Alteration in breast development after dioxin exposure has also been seen in animal studies. Suppression of the mammary gland development has been seen in TCDD-exposed animals (6). In other animal studies, in utero and lactational exposure was associated with reduced primary branches, decreased epithelial elongation, and increased number of terminal end buds and lateral branches in the breast (7-9). Longer term effects of these disturbances in the developing breasts of humans are uncertain and data on the incidence of neoplasm of the breast are inconclusive (10). In the Seveso Women's Health Study, however, a significant relation was found between serum TCDD levels and breast cancer incidence in women exposed by the Seveso incident (11).
Our study results provide more evidence that significant effects on the (human) reproductive system occur following exposure to even background levels of dioxins.

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Reference List

(1) Pluim HJ, Koppe JG, Olie K, van der Slikke JW, Slot PC, van Boxtel CJ. Clinical laboratory manifestations of exposure to background levels of dioxins in the perinatal period. Acta Paediatr 1994; 83(6):583-587.

(2) Ilsen A, Briet JM, Koppe JG, Pluim HJ, Oosting J. Signs of enhanced neuromotor maturation in children due to perinatal load with background levels of dioxins. Follow-up until age 2 years and 7 months. Chemosphere 1996; 33(7):1317-1326.

(3) ten Tusscher GW, de Weerdt J, Roos CM, Griffioen RW, De Jongh FH, Westra M et al. Decreased lung function associated with perinatal exposure to Dutch background levels of dioxins. Acta Paediatr 2001; 90(11):1292-1298.

(4) ten Tusscher GW, Steerenberg PA, van Loveren H, Vos JG, dem Borne AE, Westra M et al. Persistent hematologic and immunologic disturbances in 8-year-old Dutch children associated with perinatal dioxin exposure. Environ Health Perspect 2003; 111(12):1519-1523.

(5) Den Hond E, Roels HA, Hoppenbrouwers K, Nawrot T, Thijs L, Vandermeulen C et al. Sexual maturation in relation to polychlorinated aromatic hydrocarbons:

Sharpe and Skakkebaek's hypothesis revisited. Environ Health Perspect 2002; 110(8):771-776.

(6) Brown NM, Lamartiniere CA. Xenoestrogens alter mammary gland differentiation and cell proliferation in the rat. Environ Health Perspect 1995; 103(7-8):708-713.

(7) Brown NM, Manzolillo PA, Zhang JX, Wang J, Lamartiniere CA. Prenatal TCDD and predisposition to mammary cancer in the rat. Carcinogenesis 1998; 19(9):1623-1629.

(8) Fenton SE, Hamm JT, Birnbaum LS, Youngblood GL. Persistent abnormalities in the rat mammary gland following gestational and lactational exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Toxicol Sci 2002; 67(1):63-74.

(9) Lewis BC, Hudgins S, Lewis A, Schorr K, Sommer R, Peterson RE et al. In utero and lactational treatment with 2,3,7,8-tetrachlorodibenzo-p-dioxin impairs mammary gland differentiation but does not block the response to exogenous estrogen in the postpubertal female rat. Toxicol Sci 2001; 62(1):46-53.

(10) Birnbaum LS, Fenton SE. Cancer and developmental exposure to endocrine disruptors. Environ Health Perspect 2003; 111(4):389-394.

(11) Warner M, Eskenazi B, Mocarelli P, Gerthoux PM, Samuels S, Needham L et al. Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. Environ Health Perspect 2002; 110(7):625-628.