Toxic effects of dioxins, PCBs and PBDEs in adolescents

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Chapter 4

Influence of PCBs and dioxins on puberty; a review

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The influence of perinatal and current dioxin and PCB exposure on puberty: a review

Introduction
Polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and polychlorinated biphenyls (PCBs) belong to the group of most dangerous environmental toxicants. PCDDs, PCDFs and planar PCBs are often grouped together as ‘dioxins’ or ‘dioxin-like compounds’, because of their common mode of (toxic) action.

From the 1930’s the production of PCBs drastically increased world-wide, reaching a maximum in the 1970-80’s (1), owing to the increased use of their extreme stability and resistance to acids, bases, hydrolysis and heat. With the exception of very small quantities produced for research purposes, PCDDs/PCDFs are unwanted by-products, of the production of chlorinated phenols, metallurgic processes, bleaching of paper pulp and the incineration of waste (2,3,4).

Since the 1930’s large amounts of these compounds have been released into the environment. Organisms, and ultimately humans, are exposed via ingestion (food, drinking water), via inhalation, and via dermal contact. Ingestion is the main source (90%) of exposure in Europe, primarily through meat and meat products (23-27%), dairy products (17-27%) and fish (16-26%) (5). Due to the accumulating properties of these compounds, each step higher in the food chain increases the concentration of dioxins in an organism (bioaccumulation). Once ingested, dioxins and PCBs are primarily stored in adipose tissue and liver, the result of their hydrophobic nature.

The first measurement of dioxins in humans was carried out in 1956, when a chemist contaminated himself with tetrachlorodibenzo-p-dioxin (TCDD) and tetrabromodibenzo-p-dioxin (6). Currently, background levels of these compounds have been found throughout the industrialised world. The half life of each PCB and dioxin congener varies. The mean half-life of dioxins and PCBs in the human body is assumed to be 7 to 9 years (7), but may be shorter (8,9), however, life-long accumulation occurs.

Dioxins and PCBs are able to cross the placenta. In addition, they are excreted in breast milk and thereby cause significant exposure to nursing offspring (10). Exposure during the foetal and nursing period of a child, are considered to be the most sensitive exposure windows in terms of reproductive effects (11,12,13,14). Adolescents, undergoing hormonal changes during puberty, are probably also at greater risk of susceptibility, and therefore at higher risk, with regards to environmental exposure health effects (15).

Dioxins and PCBs interact with hormonal pathways and are therefore known as hormone and growth disruptors. They possess the potential to interfere with a multitude of biological functions. These compounds may alter the (developing) reproductive system by estrogenic or anti-estrogenic properties or by interfering with thyroid homeostasis. Dioxin-like compounds (PCDDs/Fs and planar PCBs) are able to bind to the AhR- receptor and are thereby considered to behave like anti-estrogens. However, a recent study showed that some dioxin-like compounds can have estrogenic properties as well (16). Some (non-planar) PCB congeners are considered to be estrogenic; however, the in vitro estrogen receptor (ER) binding appears weak in some studies (17,18). PCBs and their hydroxylated metabolites are also known for their effects on the thyroid regulatory pathway, both reducing and increasing serum thyroid hormone (T4) level PCBs and their hydroxylated metabolites are also known for their effects on the thyroid regulatory pathway, both reducing and increasing serum thyroid hormone (T4) levels by a variety of mechanism or combinations of mechanisms (18). Thyroid hormone is essential for normal body metabolism, growth, and development including reproduction, maturation and ageing. Fluctuations in thyroid hormone levels are able to alter reproductive outcomes in children (19).

Mice studies showed earlier sexual maturation in females and an increased number of genital abnormalities in males, after exposure to estrogenic endocrine disrupting chemicals (20,21,22). Delayed breast development in rats was found following TCDD exposure (23).

Various studies have looked at the effects on human development following perinatal exposure; some of these study cohorts were exposed to high concentrations as a result of chemical accidents, the most
important accidents being the Yusho, Seveso, Yucheng and Agent Orange incidents. For explanation of the accidents see part B.

Yet, background concentrations, concentrations that average individuals are daily exposed to, in Europe and the US, have also been related to various negative health effects. Studies have shown negative effects on lung function (24,25), and haematological and immunological disturbances (26,27,28). In addition, an increase in behavioural problems was seen and possible indications of subtle neurological influences were found in children (29,30,31,32).
In this review we summarise the most important results of studies performed on the relationship between exposure to dioxin-like compounds and PCBs and pubertal end-points in humans. Most of the studies are based on cohorts exposed to extremely high concentrations of PCBs/dioxins, following the above mentioned chemical accidents.

Materials and methods
A literature search was performed in Pubmed for references to PCB, dioxin and furan exposure and puberty development. MeSH terms and keywords used included, ‘menarche’, ‘tanner scale’, ‘pubertal development’, ‘testis’ and ‘penis’, all in combination with the MESH terms ‘PCB’ and ‘dioxin’. We focused exclusively on human studies available to the broad public via medical literature. All the articles found by this search, and linked ‘related articles’ were considered. Publications related to abnormalities caused by other disturbances than PCBs or dioxins were excluded. Articles related to exposure to PCBs or dioxins considering other endpoints than the reproductive system were also excluded.
The results from the various articles were compared. For determination of the effects on puberty caused by PCBs and dioxins, Tanner Scale, height, weight, age at menarche, testicular volume and genital abnormalities were used as end-points.

Results
The results for boys and girls will be discussed separately.
We found 4 studies focussing on pubertal development in relation to dioxins and PCBs. One of these studies focused on males exclusively. Five studies evaluated age at menarche and five studies assessed testicular volume. Only one study evaluated penis length.

Girls; Tanner scale, height, weight and age at menarche
In a North Carolina study 594 children (316 girls) were contacted and asked about their height, weight, and stage of pubertal development (Tanner) through annual mailed questionnaires. In this cohort the effects of background exposure (prenatal and lactational) to PCBs and p,p'-DDE (1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene, DDE) on pubertal growth and development were studied. Girls with the highest trans-placental PCB exposures (≥ 3 ppm =μg/g) were heavier for their heights than girls with PCB exposure of 0-1 ppm=μg/g lipids, by an average of 5.4 kg. However this difference was only significant when analysis was restricted to Caucasian girls. There were also indications that the girls with the highest PCB exposures reached the early stages of puberty sooner, however the differences were not significant. The trans-placental exposures seemed to have a greater effect on the outcomes than the lactational effects. Formula-fed girls seemed to mature later, but again this was not statistically significant. No relation was seen between lactational or trans-placental PCB exposure and age at menarche. Similarly, no relation was found between trans-placental and/or lactational DDE exposure and age at menarche (33).

A Belgian study with a cross sectional design investigated the effect of polychlorinated aromatic hydrocarbons on sexual maturation. Serum concentrations of PCB 138, 153 and 180, and dioxin-like compounds, were measured in 200 adolescents (120 females and 80 males) from two polluted suburbs of Antwerp (Hoboken and Wilrijk) and from 100 adolescents (60 girls and 40 boys) in a rural control area (Peer). In girls, a doubling of serum dioxin concentration increased the odds of not having reached the adult stage by 2.3 (34).
In a prospective longitudinal Dutch study on 33 adolescents (19 girls) puberty development was compared with perinatal PCDD/F exposure and current serum PCDD/Fs, dl-PCBs and PBDEs, in a dose-response manner. A delay in initiation of breast development was found in girls (n=18) with higher prenatal (p=0.023) and lactational PCDD/F exposure (p=0.048). The males revealed a negative trend with age at first ejaculation. For other endpoints on puberty and growth (pubic hair, axillary hair, genital stage, length, BMI, testicular volume, menarche) no significant relation was found with any of the measured compounds (35).

In this study physical examination and Tanner stages were evaluate by the same physician. Questionnaires were completed in face-to-face interviews with the adolescents and their parents.

In a Michigan cohort of people were exposed to a fire retardant during an industrial accident in 1973, the pubertal development, using the Tanner stages, was compared to serum polybrominated biphenyls (PBB), PCB (Aroclor 1254) and maternal PCB in 201 daughters, aged 5-17 years. The Tanner stage was reported via questionnaires. Maternal initial serum PCB levels were used as the maternal serum PCB levels during pregnancy, regardless of the time since the daughter’s birth. The mean in utero exposure level was estimated as 5.6 ng/g lipids. For estimation of this exposure, hazard models were used. No significant association was seen between serum PCB concentrations and Tanner scale. Perinatal PBB exposure was associated with earlier pubic hair development in breastfed girls. No association was found between the PCB exposure levels and age at menarche. Only girls exposed to high levels of PBB in utero had an earlier age at menarche (mean age 11.6 years) compared to lower exposed (mean age 12.2-12.6 years) (36).

In another study of the Michigan cohort, female participants and their offspring were studied. DDE and PCB levels had been determined previously in the serum of the mothers. The age at menarche was retrospectively assessed in the 151 female offspring, aged 20–50 years at the time of the study. Based on repeated maternal serum measurements between 1973 and 1991, the PCB and DDE serum levels at the time of pregnancy were derived. An increase in the in utero DDE exposure of 15 µg/L reduced age at menarche by 1 year. However, there was no association with maternal PCB exposure (37).

Warner et al reported age at menarche among the 282 Seveso Women’s Health Study (SWHS) participants who were pre-menarcheal at the time of the explosion. The age at menarche was compared with serum levels of TCDD in the women. The mean age of menarche in this cohort was 12.8 years. No relationship was seen between the age at menarche and the serum TCDD in the cohort (38).

In a correspondence re-evaluation of the study however, Wolff and Britton suggested that children younger than 5 years were more susceptible to hormonal effects of environmental contaminants. When Warner and Eskenazi re-evaluated the study using age stratification, they found that the children exposed before 5 years of age, may have been at increased risk for earlier menarche (39).

**Boys; tanner scale, height, weight, testicular volume and penis length**

The North Carolina cohort showed no significant PCB effects on height or weight. The boys revealed no significant pattern of early maturation, in relation to higher trans-placental exposure to PCBs. However, higher trans-placental DDE exposure was associated with increased height and weight. Boys with the highest exposure were 6.3 cm taller and 6.9 kg heavier than those with the lowest (33).

In a puberty study of Yucheng victims, 60 Yucheng boys and 60 controls were examined. Tanner status, testicular size and serum hormone (LH, PRL, T4, T3, and TSH) levels were not statistically different between Yucheng and control boys in the subgroups of before and at the age of puberty. However, the serum estradiol (E2) levels were significantly higher in Yucheng boys at the age of puberty, and there was a decrease in serum testosterone (TT) levels and increase in serum follicle-stimulating hormone (FSH) levels in Yucheng boys at the age of puberty, as compared with the controls.

The testicular volume of boys prenatally exposed to PCBs and PCDFs was unaffected (40).

In the aforementioned Dutch study, the males (n=14) revealed a negative trend with age at first ejaculation. For other endpoints on puberty and growth (pubic hair, axillary hair, genital stage, length, BMI, testicular volume) no significant relation was found with any of the measured compounds.

As mentioned above, the Antwerp study measured serum PCBs (congeners 138, 153 and 180) and
dioxin concentrations in a total of 120 boys in Wilrijk, Hoboken and Peer (control). Height, weight and Tanner scale were measured. The PCB congeners, when individually evaluated, showed congener 138 to be inversely correlated to male genital development. Similarly, concentrations of congeners 153 and 180 were inversely correlated to pubic hair growth.

In other words, a higher exposure resulted in inhibited sexual development. For measuring the testicular volume a Prader’s orchidometer was used. Although left and right testicular volume was lower in both polluted areas than in the control area (42.4 ml vs. 47.3 ml.), no relation was seen with the current PCB and dioxin-like compounds. Serum hormone concentrations (testosterone, SHBG, inhibin B, LH and FSH) were all within the normal ranges and did not differ between the areas.

Similarly, in a study of 305 young average Swedish men 18-21 years of age, lipid-adjusted serum levels of 2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB-153) were measured and correlated to markers of male reproductive function. No association between PCB-153 and testicular volume was seen (41).

Similarly, in Henriksen's study on Agent Orange veterans, no association was found between serum TCDD levels and testicular volume or testicular abnormalities (42).

**Penile length**

Fifty-five pairs of Yucheng boys and their controls were measured for penile length. Boys aged 11 to 14, who were born in the earlier years after the mothers’ intoxication, had normal progression through the Tanner stages but reduced penile length compared to that of their controls (43,44). It was hypothesised that the effects of PCBs (and PCDFs) on the length of penis might be due to hormonal effects of the toxins, since animals exposed to these chemicals exhibit hormone dysfunction and altered sexual maturation (43). While often cited, this study remains the only such study of penile length performed to date.

**Discussion**

In the North Carolina study, girls with lower PCB exposure had the tendency to mature earlier, but these differences were not significant. However, the body weight of the subjects was significantly correlated to the trans-placental PCB exposure. A weak point of this study is that the height and weight were measured by the subjects themselves and the tanner scale was determined by questionnaires filled in by the subjects themselves. A strong point of the study is the prospective longitudinal character. Unfortunately in this paper no clear indication of the congener pattern of the different measured PCBs was given and possible correlations with individual PCB congeners was not reported.

The Antwerp study showed no correlation between weight and PCB exposure in boys and girls. However, the serum concentrations of PCB congeners 153 and 180 were inversely correlated with pubic hair growth and PCB 138 inversely with genital development in boys. Furthermore, the study showed delay of breast development in girls with a higher serum concentration of dioxins. In this study puberty development was determined by four trained school physicians, making the study more reliable.

The Michigan study revealed no significant relation between sexual maturation, weight and height, and in utero PCB exposure. For estimation of this exposure, PCBs and PBBs were measured in mother’s blood after PBB exposure. Hazard models were used to calculate the possible levels during pregnancy. For evaluation of PCB exposure aroclor 1254 was measured. Tanner scales were determined by questionnaires filled in by the subjects themselves.

The cohorts were large. Puberty assessment relied on self-reporting in two of the three studies. It is arguable that a physical examination by one and the same physician might reveal a more consistent assessment of the Tanner stage of a subject. A limitation of the Michigan study is that the in uteri and postnatal chemical exposures were not directly measured, but determined by modelling. In addition, PCB exposure in the Michigan study was assessed by measuring only one PCB. The North-Carolina study performed no evaluation of correlations between puberty development and individual congeners.

Age at menarche as an indicator of endocrine disruption was evaluated in four papers. Three of the four abovementioned papers showed no difference in the age at menarche in relation to PCB or dioxin exposure. In the two Michigan studies, DDE and PBB exposure was associated with earlier age at
menarche and a re-evaluation of the Seveso study found that the children exposed before 5 years of age, may have been at increased risk for earlier menarche. A limitation of all the studies is the retrospective recall of age of menarche. The Seveso study is the only study which evaluated TCDD exposure in relation to age at menarche. The five studies mentioned above considering testicular volume, all showed no relation between concentrations of PCBs, dioxin-like compounds and testicular volume. In other words, neither high nor low and neither acute nor chronic exposure could be shown to result in testicular volume changes. Effects on breast development were seen in two studies. A study in mice showed an important role for the Ah-receptor (AhR) in normal mammary development. The AhR is expressed and immunohistochemically localised in the epithelial portions of the mouse mammary gland during periods of ductal proliferation. Treatment of mammary gland explants with TCDD resulted in suppressed lobule development of the glands (45,46).

The onset of puberty, including the physical growth spurt and development of secondary sexual characteristics, is controlled by complex neuro-endocrine mechanisms. Puberty changes occur as a consequence of the activation of the hypothalamic-pituitary-gonadal (HPG) axis and the hypothalamic-pituitary-adrenal (HPA) axis. The HPG axis is under control of both inhibitory and stimulatory mechanisms. Puberty is marked by the reactivation of the HPG axis after a low-activity state during childhood, leading to a rise in pulsatile secretion of LH and FSH from the anterior pituitary, which leads to stimulation of the gonads (47). The pubertal period is also characterised by the adrenarche, leading to pubarche (forming of pubic hair), acne and body odour, an independent physiologic effect during puberty (48).

In each step of the mechanism leading to activation of puberty, dioxin-like compounds and PCBs may interfere. It is not yet clear in which step(s) and how these compounds interfere with the normal initiation of pubertal development. On the one hand, xeno-estrogens, like some of the PCB congeners, may impair sexual maturation in men, not only by decreasing the testosterone secretion by the testis, but also through direct interference with the androgen receptor. On the other hand, dioxins and planar PCBs disturb the hormonal balance, mainly through interaction with the Ah receptor, which may influence the synthesis of hormones or their transport proteins (18).

In the above mentioned studies, varying results are seen. It must be borne in mind that PCB exposure in humans represents exposure to a mixture of different congeners, not necessarily acting in the same manner: some congeners display estrogenic effects whilst others have anti-estrogenic effects. In short, different dioxin and PCB congeners show different effects through different mechanisms of action, whether through inhibition, stimulation or synergism. An explanation for the varying results seen in different studies may also be sought in the study-limitations. The varying results seen probably emphasise the different mechanisms of influence by different endocrine disrupters. Finally, concomitant exposure to other pollutants such as furans, polybrominated aromatic hydrocarbons, phthalates and alkyl phenols, which may exert estrogenic, anti-estrogenic or androgenic effects, may also play a role.

**Conclusion**

Summarising, it can then be concluded that effects on puberty in PCB/dioxin-exposed human populations have been seen, not only in highly exposed cohorts, but also in average populations with background exposures. Effects seen in relation to PCB exposure include increased weight, a delay in pubic hair growth and male genital development in boys, sex-hormone homeostasis, reduced penis length, and delayed age at first ejaculation. Effects seen after dioxin exposure include retarded initiation and stage of breast development in girls, earlier menarche, and disruption of sex hormone homeostasis and reduced penis length in boys. That background concentrations of dioxin-like compounds and PCBs have effects on the reproductive development, in people not living in "contaminated" areas, is disconcerting and warrants further research.

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<table>
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<tr>
<th>End-point</th>
<th>Author</th>
<th>Cohort</th>
<th>Relevant results</th>
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<tbody>
<tr>
<td>Pubertal development and age at menarche</td>
<td>Gladen et al 2000</td>
<td>North Carolina; 594 children</td>
<td>(Caucasian) Girls with higher (transplacental) PCB exposure were heavier for their heights by on average 5.4 kg. There were (non-significant) signs that girls and boys with higher PCB exposure reach puberty earlier. No relation to transplacental PCB concentration and age at menarche.</td>
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<td></td>
<td>Blanck et al 2000</td>
<td>Michigan; 201 daughters (5-17 yrs) of exposed mothers</td>
<td>No association with transplacental PCB concentration and Tanner scale. (PBB showed effects on pubic hair/breast development) No relation between transplacental PCB concentration and age at menarche (only girls with higher in utero PBB exposure had menarche at an earlier age).</td>
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<td></td>
<td>Den Hond et al 2002</td>
<td>Antwerp; 200 adolescents and 100 controls</td>
<td>The serum PCBs were inversely correlated with pubic hair growth and breast stage. In girls, doubling serum dioxin increased the odds of not having reached adult stage by 2.3. PCB congener 138 in serum was inversely correlated with male genital development; PCB 153 and 180 were inversely correlated with pubic hair growth.</td>
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<td></td>
<td>Warner et al 2004</td>
<td>Seveso; 282 women premenarcheal at time of explosion</td>
<td>No relation with TCDD exposure and age at menarche.</td>
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<td></td>
<td>Warner, Eskenazi 2005 / Wolff, Britton 2005</td>
<td>Re-evaluation of the Seveso cohort; 84 women &lt; 5 years of age at time of explosion</td>
<td>Some evidence for increased risk for earlier menarche in relation to TCDD exposure.</td>
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<td></td>
<td>Hsu et al 2005</td>
<td>Yucheng: 60 Yucheng boys and 61 controls</td>
<td>A relation between PCB/PCDF and sex hormone homeostasis at puberty was seen.</td>
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<td></td>
<td>Leijis et al 2008</td>
<td>Netherlands: 33 adolescents</td>
<td>A retarded initiation in breast development was seen in girls with higher perinatal PCDD/F exposure. A retarded first ejaculation was seen in boys with higher serum dl-PCBs.</td>
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<td></td>
<td>Den Hond et al 2002</td>
<td>Belgium: 80 boys (17 yrs)</td>
<td>Testicular volume was lower in 2 polluted areas than the control area. There was no significant relation with PCB (138, 153 and 180) and dioxin-like compounds.</td>
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<tr>
<td></td>
<td>Hsu et al 2005</td>
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<tr>
<td>Penile length</td>
<td>Guo et al 2004</td>
<td>Yucheng: 55 boys (11-14 yrs)</td>
<td>Reduced penile length in PCB/PCDF exposed boys in comparison to controls.</td>
</tr>
</tbody>
</table>

Table 1: Summary of the mentioned studies
Chapter 4. Influence of PCBs and dioxins on puberty; a review

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