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## Pollutants, Sedentarism, Circadian Rhythm and their Effects on Fertility

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**Abstract:** This presentation deals with three different and diverse subject areas which may have effects on the reproductive potential of an individual. Pollutants or environmental contaminants are compounds or chemicals which may be persistent and ubiquitous, sedentarism which is related to lifestyle and circadian rhythm which is inherent in tissues, organs or whole body.

**Keywords:** fertility, pollutants, DDE, phthalates, bisphenol-A, PBDE, circadian rhythm, sedentarism

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*Reproductive Biology Insights* 2009:2 47–52

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## Pollutants

Pollutants have been a major concern to environmentalists, public health departments, government agencies and medical societies over the years. Commercial pesticide formulations of which there are more than 50,000 provide the major contaminants to the environment. Of these contaminants the “so-called” endocrine disrupting compounds (EDCs) represent a group of chemicals of particular interest because they mimic endogenous hormones, act as hormone antagonists, modulate hormone receptor activity or alter steroidogenic pathways leading to adverse developmental and reproductive effects.<sup>1</sup> These effects depend on the timing and duration of exposure as well as the dose. Timing appears to be related to the period of organogenesis in the fetus when the developing systems are exquisitely sensitive to minute levels of EDCs. This is the critical window of susceptibility. Dose response curves for many EDCs do not follow the typical linear or nonlinear monotonic patterns. In fact, they may be either “U” or “inverted U” non-monotonic.<sup>2</sup> Recent evidence suggest that these chemical contaminants may be contributing to adverse reproductive outcomes such as infertility, spontaneous abortion, preterm labour, polycystic ovary syndrome, endometriosis, and intrauterine growth retardation in the general population.<sup>3,4</sup>

In this review consideration will be given to a few of these contaminants—p,p’ dichlorodiphenylchloroethylene (DDE), phthalates, bisphenol-A and polybrominated diphenyl ethers (PBDE, flame retardants).

## DDE

DDE is a persistent metabolite of DDT an insecticide widely known for its efficacy in eradicating mosquitoes the carriers of malaria. Although banned it is still used in underdeveloped countries. In 2006 WHO supported the use of DDT to control malaria in Africa citing the benefits outweighed the harm.<sup>5</sup> However, its persistent metabolite, DDE has been implicated in spontaneous abortions, decreased cycle length, intrauterine growth retardation, preterm birth, sexual precocity and early menopause in women and sperm abnormality in men [reviewed in 1]. A median level of 25 µg/L DDE was associated with increased risk of spontaneous abortion<sup>6</sup> or intrauterine growth

retardation.<sup>7</sup> Time to pregnancy was prolonged in daughters whose mothers had levels of DDE greater than 10 µg/L<sup>8</sup> and an association was found between serum DDE levels and decreased estrogen and progesterone.<sup>9</sup> High levels of DDE were associated with early menarche in 147 patients from developing countries compared to local controls in Belgium<sup>10</sup> implicating the use of DDT in those countries. Early menopause has also been associated with high levels of DDE.<sup>11</sup> There are few studies in men relating DDT/DDE levels with adverse testicular function [reviewed in 1]. One of the mechanisms by which DDE may act is through a non-genomic effect as shown on human granulosa-lutein cells.<sup>12</sup> However, the most common mechanism by which EDCs work is at the receptor level with antagonist or agonist effects.<sup>13,14</sup> Other mechanisms include perturbations in the hypothalamo-pituitary axis, steroidogenesis, gene expression and oxidative stress.<sup>13</sup>

## Phthalates

Phthalates are used to make plastics softer and more flexible. Products that contain phthalates include food packaging, cosmetics, fragrances, hairspray, nail polish, pharmaceuticals, building materials, paints, automobiles, children’s toys, modeling clay, cleaning products and insecticides. Exposure can occur through direct contact with products containing phthalates, through leaching of phthalates into other products, or through general environmental contamination. Early animal studies have noted an effect of phthalates on ano-genital distance.<sup>15</sup> The effect appears to be an anti-androgen receptor antagonist<sup>16,17</sup> resulting in shortened ano-genital distance, hypospadias, cryptorchidism and malformations of the accessory sex organs. This mechanism of action either individually or in combination has been demonstrated using the male rat model and the most sensitive period is in utero.<sup>18</sup> The syndrome of testicular dysgenesis in man is attributed to this EDC. Recent studies have confirmed that exposure to phthalates can lead to decreased ano-genital distance in newborn human males, a sign of anti-androgenic action<sup>19</sup> as well as hypospadias.<sup>20</sup> The latter study was carried out in southeast England where the incidence of hypospadias was higher among women exposed to hair spray containing phthalates in the workplace, indicating that minute amounts may be crossing the placenta and affecting the developing



fetus in utero. In vitro studies with human fetal testes indicate that the effect may not be through decreased testosterone production.<sup>21</sup> This is in contrast to a recent study showing that high levels of urinary PBDE metabolites were associated with decreased hormone secretion in adult men.<sup>22</sup> Phthalates have also been implicated in early breast development.<sup>23</sup> Another potential source of phthalate exposure is prescription medications<sup>24</sup> which represent one of the most widely used drugs in the United States. Thus many people including pregnant women may be exposed to high concentrations of phthalates. These substances may eventually suffer the same fate as bisphenol A used in baby bottles.

## Bisphenol A

Bisphenol A (BPA) was synthesized in 1891 and first recognized as a synthetic estrogen in the 1930s. Individual monomers of BPA could be combined to make two kinds of plastics: polycarbonate and epoxy resins. BPA-based polycarbonates are used in products such as baby bottles, water bottles, eyeglass lenses, medical equipment, toys, CDs/DVDs, cell phones, consumer electronics, household appliances, sports safety equipment, airplanes, and automobiles. Epoxy resins containing BPA are used as liners for most food and beverage cans, adhesives, industrial protective coatings, and automotive primers. BPA is also used to make dental sealants and flame retardants, and is an additive in many other widely used consumer products. It is one of the highest volume chemicals produced worldwide with a global production capacity exceeding 6 billion pounds per year. BPA has been linked to many health problems including prostate cancer, diabetes, obesity, cardiovascular disease and reproductive problems such as altered mammary gland development, breast cancer, longer cycles, accelerated puberty and recurrent miscarriage.<sup>25–27</sup> Some studies on pregnant women do indicate no adverse effects.<sup>28</sup> However, the growing body of evidence in humans as well as animals provides credence to the notion that BPA adversely affects human health.<sup>29–34</sup> The long half life of BPA makes it particularly harmful.<sup>31</sup> Effects on the brain in mice<sup>29</sup> and the influence of diet on BPA effects<sup>30</sup> also contribute to BPA's notoriety. It is known that neonates are exposed to BPA.<sup>32,33</sup> The recent demonstration that BPA can confer chemo-resistance to cancer cells is disturbing.<sup>34</sup>

Canada in 2008 became the first country to ban BPA in baby bottles. The Food and Drug Administration (FDA) in the U.S.A. maintained that BPA is safe, even though the National Toxicology Program had expressed “some concern” over BPA's effects on the brain, behavior and prostate gland in children before and after birth. The European Union also supported the FDA. Dr. R. Sharpe, head of the UK government scientific advisory body in May 2009 appealed to have a ban on BPA. At the June 2009 annual meeting of the Endocrine Society in U.S.A. members echoed the same call for a ban on BPA, emphasizing the need for a more concerted effort to eradicate the use of this chemical. This is the first time this learned society has ever issued a statement and its president Dr R. Carey said the reason was BPA affects everyone and is present in over 93% of Americans. The fact that the damage from BPA can be passed to future generations makes it a more dangerous chemical.

## Polybrominated diphenyl ethers (PBDE)

PBDEs comprise a possible number of 209 congeners and are used as flame retardants. They are persistent, bioaccumulative and ubiquitous. Because of these properties they are being found in rapidly increasing levels in tissues of humans.<sup>35</sup> Concern is being raised as a result of the doubling of PBDE levels every five years in mother's milk in the United States, Japan, Sweden and the Netherlands.<sup>36</sup> Reports that PBDEs can have adverse developmental and reproductive effects underscore this concern [reviewed in 1]. However, there has not been any human data to date to suggest that PBDEs have adverse effects on reproductive processes but the possibility remains for effects on thyroid function, steroidogenesis and anti-androgenicity since dust seems to be the major route of intake into the body.<sup>37</sup> PBDEs were found to be 10-fold higher in household dryer lint in the U.S.A. compared to Germany suggesting that their effects might manifest earlier in the United States.<sup>38</sup> Indeed it was recently found that a high association was present in the concentrations of PBDE in household dust and lower testosterone levels in man.<sup>39</sup> A more disturbing report found that environmentally relevant levels of PBDE alter eggshell thickness and reproductive success of American kestrels leading the authors to suggest that PBDEs may be the next PCBs.<sup>40</sup>



PBDEs are therefore compounds of emerging concern to which we have previously referred.<sup>1</sup>

## Sedentarism

With regard to a sedentary life style it is often associated with an increase in body weight. Sedentary people were defined as those expending less than 10% of their daily energy in the performance of moderate and high intensity activities (at least 4 times the basal metabolic rate).<sup>41</sup> Body mass index (BMI) or waist-hip ratio is used to describe body habitus but BMI is more common. Obesity and overweight have consequences on reproductive health and these were covered well by Dr. J. Bellver in a previous section. Obese women are generally infertile, are anovulatory and have menstrual irregularities, reduced conception rate and a reduced response to fertility treatment.<sup>42</sup> Miscarriages and maternal and perinatal complications often occur in obese women.<sup>43</sup> Sperm density is also decreased in obese men.<sup>44</sup> Ghrelin and leptin may be involved in obesity.<sup>45,46</sup> Ghrelin a hormone secreted by the stomach, may regulate food intake, body weight, pancreatic function and glucose metabolism.<sup>47</sup> Leptin is produced in body fat, is elevated in obesity and affects steroidogenesis and ovulation.<sup>48</sup> On the other hand new research suggest that obesity may be hereditary—carriers of the fat-mass and obesity-associated gene (FTO: the fat gene) are more susceptible to obesity.<sup>49</sup> In any event it is important to reduce weight by changes in life style habits or in extreme cases, surgery, in order to reverse the adverse reproductive endpoints associated with a high BMI.

## Circadian Rhythm

Circadian rhythm is an endogenous rhythm cued by the environment and controlled by the suprachiasmatic nucleus in the anterior hypothalamus—“the master biological clock”. Light is the primary regulator which acts via a retinal ganglion cell photoreceptor in the mammalian eye. Circadian rhythms occur in many organ systems. In many mammalian species the circadian clock functions through the rhythmic transcription and translation of several genes, forming an oscillatory feedback loop.<sup>50</sup> The circadian clockwork genes are expressed in all female and male reproductive tissues studied to date and even in the early conceptus. Environmental influences can affect the function of these genes. Although the

evidence for the existence of clock genes in small animals is clear the presence of similar genes in man remains to be determined. Human studies are limited to disruptions in light dark cycles. With the advent of electricity the constant exposure to light has been considered as pollution.<sup>51</sup> A review of 22 epidemiological papers looking at associations between shift work and abortion, stillbirth, preterm birth, and birth weight was carried out by Viskum et al.<sup>52</sup> No convincing associations were observed between rotating shift work or fixed nightshift and negative pregnancy outcome. Some epidemiological support was found for a relation between fixed nightshift and late abortions/stillbirth. If fixed night work for all pregnant women is avoided, seven late abortion/stillbirths a year can be prevented. Fixed night work for pregnant women should be avoided. Fixed night work may also prolong pregnancy and reduce fetal growth.<sup>53</sup> Epidemiological evidence points to an association between artificial light and cancers such as breast and prostate.<sup>54,55</sup> Women shift workers may have menstrual irregularities, miscarriages and reduced fecundability. For example, rotating shift workers in Taiwan were found to have a higher prevalence of irregular cycles.<sup>56</sup> Whether a gene component is involved in these processes in man remains to be determined.

In conclusion, the evidence for adverse effects of environmental pollutants on human reproduction while limited in extent, favors the adoption of the precautionary principle on the basis of animal studies. Sedentary life style and its consequent overweight condition need to be addressed to achieve successful fertility. Circadian rhythm genes and human reproduction remain an area for fruitful and worthwhile investigations.

## Disclosure

The authors report no conflicts of interest.

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