

## **Endocrine Disruptors and Prostate Cancer Risk**

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Prostate cancer is the most common solid cancer in males and is the second leading cause of cancer deaths in American men (Jemal *et al.*, 2008). While rates today are markedly higher than rates observed three decades ago, the most recent statistics show that prostate cancer incidence rates have now stabilized which is thought to reflect changes in utilization of prostate specific antigen (PSA) testing. In addition, benign prostatic hyperplasia (BPH) is the most common benign neoplasm, occurring in ~ 50% of all men by the age of 60. Despite extensive research, the basis for these high rates of abnormal prostatic growth is not well understood. It is recognized, however, that steroids play a role in the initiation and progression of prostate cancer which is the basis for hormonal treatment strategies. Eunuchs do not develop prostatic carcinoma (Moore, 1947) and regression of the cancer can be initially achieved by castration and androgen blockade (Huggins & Hodges, 1941). In addition to androgens, estrogen involvement in the etiology of BPH and prostatic cancer has been postulated and the use of antiestrogens has been recently recognized to have a therapeutic role in prostate cancer management (Raghow *et al.*, 2002, Steiner & Pound, 2003, Smith, 2008 #3236). Human and rodent prostates express both estrogen receptor  $\alpha$  (ER $\alpha$ ) and estrogen receptor  $\beta$  (ER $\beta$ ) during development and into adulthood with ER $\alpha$  primarily found in stromal cells (Prins & Birch, 1997, Schulze & Claus, 1990) and ER $\beta$  in differentiated epithelium (Enmark *et al.*, 1997, Prins *et al.*, 1998). Furthermore, it is believed that early prostatic developmental events which are regulated by steroids may be linked to the predisposition of this structure to high rates of disease in adult men (Henderson B.E. *et al.*, 1991, Henderson B E *et al.*, 1988). It is noteworthy that relative

to adult estrogenic responses, the prostate gland is particularly sensitive to estrogen exposures during the critical developmental period (Prins *et al.*, 2007).

The established risk factors for prostate cancer are age and race with African American men possessing the highest incidence of prostate cancer world-wide, at rates two-fold of those for Caucasian-American counterparts. It is also recognized that genetics (family history), diet and environmental factors can impact prostate cancer risk. In the human population, direct connections between endocrine disruptors (EDs) and prostate cancer risk has not been established. Nonetheless, due to the hormonal basis of this disease and the evidence that dietary compounds high in isoflavones (e.g. red clover, genistein) can control prostate cancer growth in humans (Jarred *et al.*, 2002, Lakshman *et al.*, 2008) and animal models (McCormick *et al.*, 2007), there is reasonable cause to evaluate and understand any potential relationship between environmental endocrine disruptors and prostate cancer risk. In addition to epidemiologic studies, there are *in vitro* studies with human prostate cells and *in vivo* studies in animal models that indicate associations between EDs and prostate cancer, carcinogenesis and/or susceptibility. Due to difficulties in directly associating prostate cancer risk in humans with ED exposures, potential risk(s) will have to include research with animal models, particularly those that are responsive to environmentally relevant exposures.

### **Evidence and Mechanisms:**

#### **Farming and Pesticides**

Regarding links between prostate cancer and environmental factors in humans (outside of diet), the most compelling data comes from the established occupational

hazard of farming and increased prostate cancer rates (Alavanja *et al.*, 2003, Meyer *et al.*, 2007, Morrison *et al.*, 1993). While several variables may contribute to higher prostate cancer rates in farmers, chronic or intermittent exposures to pesticides is the most likely explanation (Alavanja *et al.*, 2003, Van Maele-Fabry *et al.*, 2006). This is supported by a large epidemiology study (Agricultural Health Study) in a collaborative effort between the NCI, NIEHS and EPA in the United States that has examined agricultural lifestyles and health in ~90,000 participants in North Carolina and Iowa since 1993 ([www.aghealth.org](http://www.aghealth.org)). Evaluation of >55,000 pesticide applicators revealed a direct link between methyl bromide exposure, a fungicide with unknown mode of action, and increased prostate cancer rates. Further, six pesticides out of 45 common agricultural pesticides showed correlation with exposure and increased prostate cancer in men with a familial history, suggesting gene-environment interactions. These six agents were chlorpyrifos, fonofos, coumaphos, phorate, permethrin and butylate (Alavanja *et al.*, 2003, Mahajan *et al.*, 2006). The first four of these compounds are thiophosphates and share a common chemical structure. While these agents are regarded as acetylcholine esterase inhibitors and have not been shown to have direct estrogenic or antiandrogenic activities, a literature search revealed that these compounds have significant capacity as p450 enzyme inhibitors. In particular, chlorpyrifos, fonofos and phorate strongly inhibit CYP1A2 and CYP3A4 which are the major p450s that metabolize estradiol, estrone and testosterone in the liver (Usmani *et al.*, 2003, Usmani *et al.*, 2006). Furthermore, the human prostate constitutively expresses CYP1A2 and CYP3A4 enzymes that are involved in intraprostatic metabolism of steroids, drugs and dietary compounds (Lawson *et al.*, 2002; Finnstrom *et al.*, 2001, Sterling *et al.*, 2004]. This raises the possibility that exposure to these compounds may interfere with

steroid hormone metabolism by the liver as well as the prostate and, in so doing, alter steroid balance and availability which in turn may contribute to increased prostate cancer risk. A similar mechanism of endocrine disruption *in vivo* has been identified for PCBs and polyhalogenated aromatic hydrocarbons (including dioxins, BPA and dibenzofurans) through potent inhibition of estrogen sulfotransferase which effectively elevates bioavailable estrogens in various target organs (Kester *et al.*, 2002, Kester *et al.*, 2000).

### Environmental Estrogens:

In men, chronically elevated estrogens have been associated with increased risk of prostate cancer (Modugno *et al.*, 2001). In rodents, estrogens in combination with androgens induce prostate cancer (Leav *et al.*, 1988). For the sake of simplicity, we here refer to environmental estrogens as molecules with identified estrogenic activity (estrogen mimics), mostly through activation of estrogen receptors.

DES: Diethylstilbestrol exposure is considered an important model of endocrine disruption and provides proof-of-principle for exogenous estrogenic agents as disruptors of multiple end-organs. Maternal exposure to DES during pregnancy was found to result in more extensive prostatic squamous metaplasia in human male offspring than observed with maternal estradiol alone (Driscoll & Taylor, 1980). While prostatic metaplasia eventually resolved following DES withdrawal, ectasia and persistent distortion of ductal architecture remained (Yonemura *et al.*, 1995). This has led to the postulation that men exposed prenatally to DES may be at increased risk for prostatic disease later in life although this has not been borne out in the limited population studies conducted to date (Giusti *et al.*, 1995). However, extensive studies with DES in rodent models predict marked abnormalities in the adult prostate including increased

susceptibility to adult-onset carcinogenesis following early DES exposures (Arai *et al.*, 1983, Huang *et al.*, 2004, Prins *et al.*, 2001, Rajfer & Coffey, 1978).

BPA: Bisphenol A is a synthetic polymer used in the production of polycarbonate plastics and epoxy resins and significant levels have been found in the urine of 93% of US population in a recent screen by the CDC (Calafat *et al.*, 2008). The relative binding affinity of BPA for either estrogen receptor (ER $\alpha$  and ER $\beta$ ) and capacity for BPA to activate ER-dependent transcription is ~10,000 lower than estradiol or diethylstilbestrol (Kuiper *et al.*, 1998), (Lemmen *et al.*, 2004). While these data might suggest that BPA has minimal estrogenic activity, 1  $\mu$ M BPA is 50% as efficacious as 1  $\mu$ M 17 $\beta$ -estradiol in activating an estrogen responsive luciferase reporter (Kurosawa *et al.*, 2002). This indicates that, although BPA may have a significantly lower potency than endogenous estrogens *in vitro*, it is a full agonist for both ER $\alpha$  and ER $\beta$ . Furthermore, BPA induces ER through non-genomic pathways with an EC<sub>50</sub> equivalent to 17 $\beta$ -estradiol suggesting that *in vivo* estrogenic activity of BPA may be due to non-genomic activation of ER (Song *et al.*, 2002, Walsh *et al.*, 2005).

Effects of BPA with regards to carcinogenic potential, including the prostate gland, have recently been reviewed by an expert panel (Keri *et al.*, 2007). In short, there is evidence from rodent models and human prostate cell lines that BPA can influence carcinogenesis, modulate prostate cancer cell proliferation and for some tumors, stimulate progression. Recent reports have provided evidence that early life exposure to BPA may increase susceptibility to hormonal carcinogenesis in the prostate gland, possibly by developmentally reprogramming carcinogenic risk (Ho *et al.*, 2006, Prins *et al.*, 2008). Studies using a rat model showed that brief neonatal exposure to a low dose

of BPA (10  $\mu\text{g}/\text{kg}$  BW/day) significantly increased the incidence and grade of prostatic intraepithelial neoplasia (PIN) following adult estrogen exposure. This model of sensitivity to hormonal carcinogenesis is relevant to humans in that relative estradiol levels increase in the aging male and may contribute to prostate disease risk (Kaufman & Vermeulen, 2005). The above studies further identified alterations in DNA methylation patterns in multiple cell signaling genes in BPA-exposed prostates which suggests that environmentally relevant doses of BPA “imprint” the developing prostate through epigenetic alterations (Ho *et al.*, 2006, Prins *et al.*, 2008).

Knudsen and colleagues examined the influence of BPA on human prostate cancer cells that contained an AR point mutation (AR-T877A) frequently found in advanced prostate cancers of patients who relapsed after androgen deprivation therapy (Wetherill Y B *et al.*, 2005). They first observed that 1 nM BPA activates AR-T877A in transcriptional assays and leads to unscheduled cell cycle progression and cellular proliferation *in vitro* in the absence of androgen. Since BPA had no impact on wild type AR, these data indicate that this gain-of-function AR mutant attained the ability to utilize BPA as an agonist. Subsequent *in vivo* analyses of the impact of BPA on human prostate tumor growth and recurrence was performed utilizing a mouse xenograft of human cells containing the AR-T877A mutation (Wetherill Y.B. *et al.*, 2006). At low doses that fall within the reported ranges of human exposure, prostate tumor size increased in response to BPA administration as compared to placebo control and mice in the BPA cohort demonstrated an earlier rise in PSA (biochemical failure). These findings indicating that BPA significantly shortened the time to therapeutic relapse.

These outcomes underscore the need for further study of the effects of BPA on tumor progression and therapeutic efficacy.

PCBs: Persistent organic pollutants, such as polychlorinated biphenols (PCBs) are fat soluble chemicals that bioaccumulate in the human body. Many have estrogenic or antiandrogenic activity and as such, may perturb male reproductive activity. A recent analysis of adipose tissue concentrations of PCBs in Swedish men with and without prostate cancer revealed a significant association between PCB levels in the higher quadrants and prostate cancer odds ratio with the most marked associations for PCB153 and trans-chlordane (Hardell *et al.*, 2006). A more extensive epidemiologic study of capacitor manufacturing plant workers highly exposed to PCBs revealed a strong exposure-response relationship for prostate cancer mortality (Prince *et al.*, 2006). This supports previous findings of correlations between PCB 153 and 180 and prostate cancer risk in electric utility workers (Charles *et al.*, 2003, Ritchie *et al.*, 2003). While estrogenic activity of these compounds is a suspected mode of action, there is also evidence that PCBs inhibit estrogen sulfotransferase activity in the liver and effectively increase bioavailable estrogen in the body (Kester *et al.*, 2000). Recently, Aroclor-1254, a mixture of 60 PCB pollutants, was tested on rat prostate cells *in vitro* and shown to disrupt gap junctions, expression of connexin 32 and 43 and increase double-stranded DNA breaks suggesting that PCBs may be able to transform prostate cells leading to carcinogenesis (Cillo *et al.*, 2007). Further investigation using animal models is warranted for PCBs and prostate cancer risk.

UV filters: There are a few recent reports that ultra violet light filters that are used to protect against the sun have estrogenic activity (Schlumpf *et al.*, 2004b). Specifically,

4-methylbenzylidene camphor (4-MBC) and 3-benzylidene camphor (3-BC) are ER $\beta$  ligands (Schlumpf *et al.*, 2004a). While little if any work has been done with regards to these UV filters and human prostate cancer, a few recent reports indicate that developmental exposure to the compounds can alter prostate gland development and estrogen target gene expression in the rat (Hofkamp *et al.*, 2008, Schlumpf *et al.*, 2004b). This raises the possibility that the fetal prostate may be affected following maternal use of these compounds.

Cadmium: Cadmium is known to ligand to ERs and function as an estrogenic mimic. While some large epidemiologic reports have indicated a relationship between cadmium exposure and prostate cancer rates, others have refuted these findings (Parent & Siemiatycki, 2001). Nonetheless, there are intriguing reports in the literature which show that cadmium has proliferative action with human prostate cells *in vitro* through an ER-dependent mechanism and that this exposure is associated with acquisition of androgen-independence (Benbrahim-Tallaa *et al.*, 2007b). Furthermore, prostatic tumors have been shown to be experimentally induced by oral exposure to cadmium (Waalkes, 2000). Since cadmium bioaccumulates in the body, further epidemiologic analysis of cadmium and prostate cancer risk is warranted, particularly in men with occupational exposures.

Arsenic: Exposure to arsenic has long been associated with a number of diseases including cancers (Chen *et al.*, 1988, Watson & Yager, 2007). A recent review of the epidemiologic data has shown an association between inorganic arsenic exposure from the environment and prostate cancer incidence and mortality in the human population (Benbrahim-Tallaa & Waalkes, 2008). Importantly, it has been

documented that arsenic may mediate some of these effects through endocrine disruption, specifically through interaction with ERs and activation of estrogen-regulated genes (Davey *et al.*, 2007). In this context, there is a recent report that arsenic can induce malignant transformation of prostate epithelial cells *in vitro* and drive them towards an androgen-independent state (Benbrahim-Tallaa *et al.*, 2007a). Interestingly, this was shown to be mediated through Ras-MAPK pathways and it is possible that membrane ERs may be involved in this process. Epidemiologic studies have shown an association between arsenic exposure and prostate cancer mortality in Taiwan (Chen *et al.*, 1988), a finding that was substantiated by a later study in the United States (Lewis *et al.*, 1999). Thus it is possible that endocrine disruption by arsenic can contribute to prostate cancer risk.

#### Antiandrogens:

While there are no known environmental androgens, endocrine disruptors can also function through anti-androgenic pathways. Since prostate cancer is an androgen-dependent disease, we will briefly examine the known effects of some of these agents on the prostate gland.

Vinclozalin: Vinclozolin is a fungicide that is used as a pesticide on crops. It has known anti-androgenic properties by interfering with androgen receptor (AR) activity (Kavlok & Cummings, 2005). Since vinclozalin effects are driven through AR antagonism, it is not surprising that there are no reported associations between this compound and prostate cancer, an androgen-dependent disease. Exposure of rats to vinclozalin during development results in reduced prostate gland growth and size which would be expected for an anti-androgen (Yu *et al.*, 2004). Of interest, however, are

recent studies with maternal (i.e. *in utero*) exposure to vinclozalin in rats which produce transgenerational effects on offspring through epigenetic alterations (Anway M D *et al.*, 2005). These permanent perturbations include adverse consequences on the prostate gland such as premature acinar atrophy and aging-associated prostatitis for four generations (Anway M. & Skinner, 2008). This may be particularly significant in light of recent evidence that chronic inflammation may play a role in prostate cancer initiation (Nelson *et al.*, 2002).

DDT/DDE: Dichlorodiphenyltrichloroethane (DDT) and its metabolic derivative p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE) were widely used as pesticides in the United States and their use is still in effect in other countries world-wide. In addition to AR antagonistic effects (Gray *et al.*, 1999), p,p'-DDE at high concentrations has been shown to function as an inhibitor of 5 $\alpha$ -reductase, the intraprostatic enzyme responsible for converting testosterone to the more potent androgen, dihydrotestosterone (Lo *et al.*, 2007). While many reproductive abnormalities have been found with DDT/DDE exposure, including reduced prostate growth, there is no known association between exposure to DDT/p,p'-DDE and prostate cancer risk .

#### Summary and Key Questions:

There is increasing evidence both from epidemiology studies and animal models that specific endocrine-disrupting compounds may influence the development or progression of prostate cancer. In large part, these effects appear to be linked to interference with estrogen signaling, either through interacting with ERs or by influencing steroid metabolism and altering estrogen levels within the body. In humans, epidemiologic evidence links specific pesticides, PCBs and inorganic arsenic exposures

to elevated prostate cancer risk. Studies in animal models also show augmentation of prostate carcinogenesis with several other environmental estrogenic compounds including cadmium, UV filters and BPA. Importantly, there appears to be heightened sensitivity of the prostate to these endocrine disruptors during the critical developmental windows including *in utero* and neonatal time points as well as during puberty. Thus infants and children may be considered a highly susceptible population for ED exposures and increased risk of prostate cancers with aging.

There are several key questions that must be addressed in future studies in order to best appreciate and understand the risks of prostate disease as they relate to endocrine-disrupting chemicals.

1. What specific ED chemicals can influence the prostate gland and increase prostate cancer risk or progression?
2. What are their modes of action?
3. Are there epigenetic pathways that mediate developmental exposures to EDs and prostate disease with aging?
4. Is there an additive or synergistic effect from ED mixtures and prostate cancer risk or growth?
5. Does ED exposure influence prostate cancer susceptibility in subpopulations of men? Are there specific pathways with which ED chemicals synergize to influence prostate cancer incidence and/or progression?
6. Is the *in utero* developing human prostate sensitive to ED chemicals and do they influence prostate cancer risk in the aging male? What are the most appropriate life stages for examining ED and prostate cancer risk?

7. Is there a transgenerational risk for prostate cancer as a function of ED exposures?
8. Can we establish molecular markers for ED exposures as they relate to prostate disease risk?

Focused research on these and other specific questions is required in order to adequately evaluate the human risk for prostate disease from the growing accumulation of EDs in the environment. Insight into molecular mechanisms may help to provide biomarkers for prostate disease risk from ED exposure as well as to provide opportunities for therapeutic intervention.

## **REFERENCES**

- Alavanja MC, Samanic C, Dosemeci M, Lubin J, Tarone R, Lynch CF, Knott C, Thomas K, Hoppin JA, Barker J *et al.* 2003 Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. *Am J Epidemiol* **157** 800-814.
- Anway M & Skinner M 2008 Transgenerational effects of the endocrine disruptor vinclozolin on the prostate transcriptome and adult onset disease. *Prostate* **Epub ahead of print**.
- Anway MD, Cupp AS, Uzumcu M & Skinner MK 2005 Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science* **308** 1466-1469.
- Arai Y, Mori T, Suzuki Y & Bern HA 1983 Long-term effects of perinatal exposure to sex steroids and diethylstilbestrol on the reproductive system of male mammals. In *Intern'l Rev Cytol*, pp 235-268, edn. Ed. Eds GHaD Bourne, J.F. New York, New York: Academic Press, Inc.
- Benbrahim-Tallaa L & Waalkes MP 2008 Inorganic arsenic and human prostate cancer. *Envir Hlth Prospect* **116** 158-164.
- Benbrahim-Tallaa L, Webber MM & Waalkes MP 2007a Mechanisms of acquired androgen independence during arsenic-induced malignant transformation of human prostate epithelial cells. *Environ Health Perspect* **2**.
- Benbrahim-Tallaa L, Liu J, Webber MM & Waalkes MP 2007b Estrogen signaling and disruption of androgen metabolism in acquired androgen-independence during cadmium carcinogenesis in human prostate epithelial cells. *Prostate* **67** 135-145.
- Calafat AM, Ye X, Wong LY, Reidy JA & Needham LL 2008 Exposure of the U.S. population to bisphenol A and 4-tertiary-octylphenol: 2003-2004. *Envir Hlth Prospect* **116** 39-44.
- Charles LE, Loomis D, Shy CM, Newman B, Millikan R, Nylander-French LA & Couper D 2003 Electromagnetic fields, polychlorinated biphenyls, and prostate cancer mortality in electric utility workers. *Am J Epidemiology* **157** 683-691.
- Chen CJ, Kuo T & Wu M 1988 Arsenic and cancers. *Lancet* **1**.
- Cillo F, de Eguileor M, Gandolfi F & Brevini T 2007 Aroclor-1254 affects mRNA polyadenylation, translational activation, cell morphology, and DNA integrity of rat primary prostate cells. *Endocr Relat Cancer* **14** 257-266.
- Davey JC, Bodwell JE, Gosse JA & Hamilton J 2007 Arsenic as an endocrine disruptor: effects of arsenic on estrogen receptor-mediated gene expression in vivo and in cell culture. *Toxicol Sci* **98** 75-86.
- Driscoll SG & Taylor SH 1980 Effects of prenatal maternal estrogen on the male urogenital system. *Obstet Gynecol* **56** 537-542.
- Enmark E, Pelto-Huikko M, Grandien K, Lagercrantz S, Lagercrantz J, Fried G, Nordenskjold M & Gustafsson J 1997 Human estrogen receptor  $\beta$ -gene structure, chromosomal localization, and expression pattern. *JCEM* **82** 42584265.
- Finnström N, Bjelfman C, Söderström T, Smith G, Egevad L, Norlén B, Wolf CR, Rane A 2001 Detection of cytochrome P450 mRNA transcripts in prostate samples by RT-PCR. *Eur J Clin Invest* **31** 880-886.

Giusti RM, Iwamoto K & Hatch EE 1995 Diethylstilbestrol revisited: A review of the long-term health effects. *Ann Int Med* **122** 778-788.

Gray LE, Wolf C, Lambright C, Mann P, Price M, Cooper RL & Ostby J 1999 Administration of potentially antiandrogenic pesticides (procymidone, linuron, iprodione, chlozolinate, p,p'-DDE, and ketoconazole) and toxic substances (dibutyl- and diethylhexyl phthalate, PCB 169, and ethane dimethane sulphonate) during sexual differentiation produces diverse profiles of reproductive malformations in the male rat. *Toxicol Ind Health* **15** 94-118.

Hardell L, Andersson SO, Carlberg M, Bohr L, van Bavel B, Lindström G, Björnfoth H & Ginman C 2006 Adipose tissue concentrations of persistent organic pollutants and the risk of prostate cancer. *J Occup Environ Med* **48** 700-707.

Henderson BE, Ross RK & Pike MC 1991 Toward the primary prevention of cancer. *Science* **254** 1131-1136.

Henderson BE, Bernstein L, Ross RK, Depue RH & Judd HL 1988 The early in utero oestrogen and testosterone environment of blacks and whites: potential effects on male offspring. *Br J Cancer* **57** 216-218.

Ho SM, Tang WY, Belmonte J & Prins GS 2006 Developmental exposure estradiol and bisphenol A (BPA) increases susceptibility to prostate carcinogenesis and epigenetically regulates phosphodiesterase type 4 variant (PDE4D4) in the rat prostate. *Canc Res* **66** 5624-5632.

Hofkamp L, Bradley S, J. T, Lichtensteiger W, Schumpf M & Timms B 2008 Region-specific growth effects in the developing rat prostate following developmental exposure to estrogenic UV filters. *Envir Hlth Prospect* **Epub ahead of print**.

Huang L, Pu Y, Alam S, Birch L & Prins GS 2004 Estrogenic regulation of signaling pathways and homeobox genes during rat prostate development. *J Andrology* **25** 330-337.

Huggins C & Hodges CF 1941 Studies on prostatic cancer. I. The effect of castration, of estrogen, and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Can Res* **1** 293-297.

Jarred RA, Keikha M, Dowling C, McPherson SJ, Clare AM, Husband AJ, Pedersen JS, Frydenberg M & Risbridger GP 2002 Induction of apoptosis in low to moderate-grade human prostate carcinoma by red clover-derived dietary isoflavones. *Cancer Epidemiol Biomarkers Prev* **11** 1689-1696.

Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T & Thun MJ 2008 Cancer Statistics, 2008. *Ca Cancer J Clin* **58** 71-96.

Kaufman JM & Vermeulen A 2005 The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endocrine Reviews* **26** 833-876.

Kavlok R & Cummings A 2005 Mode of action: inhibition of androgen receptor function--vinclozolin-induced malformations in reproductive development. *Crit Rev Toxicol* **35** 721-726.

Keri R, Ho SM, Hunt PA, Knudsen KE, Soto AM & Prins GS 2007 An Evaluation of Evidence for the Carcinogenic Activity of Bisphenol A: Report of NIEHS Expert Panel on BPA. *Reprod Toxicol* **24** 240-252.

Kester MH, Bulduk S, van Toor H, Tibboel D, Meini W, Glatt H, Falany CN, Coughtrie MW, Schuur AG, Brouwer A *et al.* 2002 Potent inhibition of estrogen sulfotransferase by hydroxylated metabolites of polyhalogenated aromatic hydrocarbons

reveals alternative mechanism for estrogenic activity of endocrine disrupters. *J Clin Endo Metab* **87** 1142-1150.

Kester MH, Bulduk S, Tibboel D, Meini W, Glatt H, Falany CN, Coughtrie MW, Bergman A, Safe SH, Kuiper GG *et al.* 2000 Potent inhibition of estrogen sulfotransferase by hydroxylated PCB metabolites: a novel pathway explaining the estrogenic activity of PCBs. *Endocrinology* **141** 1897-1900.

Kuiper GG, Lemmen JG, Carlsson B, Corton JC, Safe SH, van der Saag PT, van der Burg B & Gustafsson JA 1998 Interaction of estrogenic chemicals and phytoestrogens with estrogen receptor beta. *Endocrinology* **139** 4252-4263.

Kurosawa T, Hiroi H, Tsutsumi O, Ishikawa T, Osuga Y, Fujiwara T, Inoue S, Muramatsu M, Momoeda M & Taketani Y 2002 The activity of bisphenol A depends on both the estrogen receptor subtype and the cell type. *Endocrine J* **49** 465-471.

Lakshman M, Xu L, Ananthanarayanan V, Cooper J, Takimoto CH, Helenowski I, Pelling JC & Bergan RC 2008 Dietary genistein inhibits metastasis of human prostate cancer in mice. *Cancer Research, submitted*. **68** 2024-2032.

Lawson T, Kolar C 2002 Human prostate epithelial cells metabolize chemicals of dietary origin to mutagens. *Cancer Lett* **175** 141-146.

Leav I, Ho S, Ofner P, Merk F, Kwan P & Damassa D 1988 Biochemical alterations in sex hormone-induced hyperplasia and dysplasia of the dorsolateral prostates of Noble rats. *J Nat'l Canc Inst* **80** 1045-1053.

Lemmen JG, Arends RJ, van der Saag PT & van der Burg B 2004 In vivo imaging of activated estrogen receptors in utero by estrogens and bisphenol A. *Envir Hlth Prospect* **112** 1544-1549.

Lewis DR, Southwick JW, Ouellet-Hellstrom R, J. R & Calderon R 1999 Drinking water arsenic in Utah: A cohort mortality study. *Envir Hlth Prospect* **107**.

Lo S, King I, Alléra A & Klingmüller D 2007 Effects of various pesticides on human 5alpha-reductase activity in prostate and LNCaP cells. *Toxicol In Vitro* **21** 502-508.

Mahajan R, Bonner MR, Hoppin JA & Alavanja MC 2006 Phorate exposure and incidence of cancer in the agricultural health study. *2006 Environ Health Perspect* **8**.

McCormick DL, Johnson WD, Bosland MC, Lubet RA & Steele VE 2007 Chemoprevention of rat prostate carcinogenesis by soy isoflavones and by Bowman-Birk inhibitor. *Nutr Cancer*. 2007;**57**(2):184-93. *Nutr Cancer* **57** 184-193.

Meyer TE, Coker AL, Sanderson M & Symanski E 2007 A case-control study of farming and prostate cancer in African-American and Caucasian men. *Occup Environ Med* **64** 155-160.

Modugno F, J.L. W, Trump DL, Zmuda JM, Shea P, Cauley JA & Ferrell RE 2001 Allelic variants of aromatase and androgen and estrogen receptors: toward a multigenic model of prostate cancer risk. *Clinical Cancer Research* **7** 3092-3096.

Moore RA 1947. In *Endocrinology of Neoplastic Disease*, p. 194, edn. Ed. Eds New York: Oxford University Press.

Morrison H, Savitz D, Semenciw R, Hulka B, Mao Y, Morison D & Wigle D 1993 Farming and prostate cancer mortality. *Am J Epidemiol* **137** 270-280.

Nelson WG, DeWeese TL & DeMarzo AM 2002 The diet, prostate inflammation, and the development of prostate cancer. *Cancer Metast Rev* **21** 3-16.

Parent ME & Siemiatycki J 2001 Occupation and prostate cancer. **23** 1.

Prince MM, Ruder AM, Hein MJ, Waters MA, Whelan EA, Nilsen N, Ward EM, Schnorr TM, Laber PA & Davis-King KE 2006 Mortality and exposure response among 14,458 electrical capacitor manufacturing workers exposed to polychlorinated biphenyls (PCBs). *Environ Health Perspect* **114** 1508-1514.

Prins GS & Birch L 1997 Neonatal estrogen exposure up-regulates estrogen receptor expression in the developing and adult rat prostate lobes. *Endocrinology* **138** 1801-1809.

Prins GS & Korach KS 2008 The Role of Estrogens and Estrogen Receptors in Normal Prostate Growth and Disease. *Steroids* **73** 233-244.

Prins GS, Birch L, Yang WY & Ho SM 2007 Developmental estrogen exposures predispose to prostate carcinogenesis with aging. *Reprod Toxicol* **23** 374-382.

Prins GS, Tang WY, Belmonte J & Ho SM 2008 Perinatal Exposure to Oestradiol and Bisphenol A Alters the Prostate Epigenome and Increases Susceptibility to Carcinogenesis. *Basic and Clinical Pharmacology & Toxicology* **102** 134-138.

Prins GS, Marmer M, Woodham C, Chang WY, Kuiper G, Gustafsson JA & Birch L 1998 Estrogen receptor- $\beta$  messenger ribonucleic acid ontogeny in the prostate of normal and neonatally estrogenized rats. *Endocrinology* **139** 874-883.

Prins GS, Birch L, Habermann H, Chang WY, Tebeau C, Putz O & Bieberich C 2001 Influence of neonatal estrogens on rat prostate development. *Reprod Fertil Dev* **13** 241-252.

Raghow S, Hooshdraran MZ, Katiyar S & Steiner MS 2002 Toremifene prevents prostate cancer in the transgenic adenocarcinoma of mouse prostate model. *Canc Res* **62** 1370-1376.

Rajfer J & Coffey DS 1978 Sex steroid imprinting of the immature prostate. *Invest Urol* **16** 186-190.

Ritchie JM, Vial SL, Fuortes LJ, Guo H, Reedy VE & Smith EM 2003 Organochlorines and risk of prostate cancer. *J Occup Environ Med.* **45** 692-702.

Schlumpf M, Jarry H, Wuttke W, Ma R & Lichtensteiger W 2004a Estrogenic activity and estrogen receptor beta binding of the UV filter 3-benzylidene camphor. Comparison with 4-methylbenzylidene camphor. *Toxicology* **199** 109-120.

Schlumpf M, Schmid P, Durrer S, Conscience M, Maerkel K, Henseler M, Gruetter M, Herzog I, Reolon S, Ceccatelli R *et al.* 2004b Endocrine activity and developmental toxicity of cosmetic UV filters--an update. *Toxicology* **205** 113-122.

Schulze H & Claus S 1990 Histological localization of estrogen receptors in normal and diseased human prostates by immunocytochemistry. *Prostate* **16** 331-343.

Song KH, Lee K & Choi HS 2002 Endocrine disruptor bisphenol A induces orphan nuclear receptor Nur77 gene expression and steroidogenesis in mouse testicular Leydig cells. *Endocrinology* **143** 2208-2215.

Steiner MS & Pound CR 2003 Phase IIA clinical trial to test the efficacy and safety of Toremifene in men with high-grade prostatic intraepithelial neoplasia. *Clin Prostate Cancer* **2** 24-31.

Sterling KM, Cutrineo KR 2004 Constitutive and inducible expression of cytochromes P4501A (CYP1A1 and CYP1A2) in normal prostate and prostate cancer cells. *J Cell Biol* **91** 423-429.

Thomas JA & Keenan EJ 1994 Effects of estrogen on the prostate. *Journal of Andrology* **15** 97-99.

Usmani KA, Rose RL & Hodgson E 2003 Inhibition and activation of the human liver microsomal and human cytochrome P450 3A4 metabolism of testosterone by deployment-related chemicals. *Drug Metab Dispos* **31** 384-391.

Usmani KA, Cho TM, Rose RL & Hodgson E 2006 Inhibition of the human liver microsomal and human cytochrome P450 1A2 and 3A4 metabolism of estradiol by deployment-related and other chemicals. *Drug Metab Dispos* **34** 1606-1614.

Van Maele-Fabry G, Libotte V, Willems J & Lison D 2006 Review and meta-analysis of risk estimates for prostate cancer in pesticide manufacturing workers. *Cancer Causes Control* **17** 353-373.

Waalkes MP 2000 Cadmium carcinogenesis in review. *J Inorg Biochem*.

Walsh DE, Dockery P & Doolan CM 2005 Estrogen receptor independent rapid non-genomic effects of environmental estrogens on [Ca<sup>2+</sup>]<sub>i</sub> in human breast cancer cells. *Mol Cell Endocrinol* **230** 23-30.

Watson WH & Yager JD 2007 Arsenic: extension of its endocrine disruption potential to interference with estrogen receptor-mediated signaling. *Tox Sci* **98** 1-2.

Wetherill YB, Fisher NL, Staubach A, Danielsen M, de Vere White RW & Knudsen KE 2005 Xenoestrogen action in prostate cancer: pleiotropic effects dependent on androgen receptor status. *Cancer Res* **65** 54-65.

Wetherill YB, Hess-Wilson JK, Comstock CE, Shah SA, Buncher CR, Sallans L, Limbach PA, Schwemberger S, Babcock GF & Knudsen KE 2006 Bisphenol A facilitates bypass of androgen ablation therapy in prostate cancer. *Mol Cancer Therapy* **5** 3181-3190.

Yonemura CY, Cunha GR, Sugimura Y & Mee SL 1995 Temporal and spatial factors in diethylstilbestrol-induced squamous metaplasia in the developing human prostate. II. Persistent changes after removal of diethylstilbestrol. *Acta Anat* **153** 1-11.

Yu W, Lee B, Nam S, Ahn B, Hong J, J. D, Kim Y, Lee Y & Yun Y 2004 Reproductive disorders in pubertal and adult phase of the male rats exposed to vinclozolin during puberty. *J Vet Med Sci* **66** 847-853.