

Hormonally active agents: summary of epidemiologic evidence

Updated February 23, 2004

1. Overall summary

This section summarizes epidemiologic evidence cited in the tables below and will be updated as new evidence becomes available. I would appreciate feedback on any errors or omissions. Potential health effects of environmental hormonally active agents are limited here to those involving the reproductive system (birth defects, pubertal development, semen quality, fertility, cancer) and thyroid function. The tables below include some epidemiologic studies also shown in tables for other chapters, particularly Chapter 6 (PCBs, Dioxins, and Related Compounds) and Chapter 7 (Pesticides). The associations with environmental toxicants described below may or may not involve hormonal and/or other mechanisms – there has been inadequate human research to establish associations between reproductive or thyroid health effects and environmental contaminants involving hormonal mechanisms. Associations with diethylstilbestrol (DES) and other hormone therapies during early pregnancy are included to illustrate the potential effects of prenatal hormone exposure.

Health effect	Level of evidence ^a	Comments
Cryptorchidism: role of prenatal maternal hormone therapy	DES Sufficient	Follow-up of the children of pregnant women who participated in a randomized clinical trial of DES showed an increased risk of urogenital birth defects among those exposed during the 1 st trimester (Beral et al. 1981). Three reviews concluded that 1 st trimester maternal DES therapy caused male reproductive tract abnormalities including cryptorchidism, hypospadias, epididymal cysts and hypotrophic testicles and penis (Giusti et al. 1995, Mittendorf 1995, Swan 2000).
	Estradiol, oral contraceptive hormones, progestins (Inadequate)	Two case-control studies of cryptorchidism found borderline (Depue 1984) or non-significant associations with prenatal estradiol or DES therapy (Beard et al. 1984); both studies showed no relationship with prenatal maternal progestin therapy. Depue et al. (1984) and McBride et al. (1991) found no association between cryptorchidism and maternal oral contraceptive use during early gestation but both studies had low statistical power for testing this association.
Cryptorchidism: role of endogenous maternal hormones	Maternal serum estradiol or testosterone (Inadequate)	Among three case-control studies of cryptorchidism and maternal 1 st trimester endogenous serum estradiol levels, there were borderline positive (Bernstein et al. 1988) and inverse (Burton et al. 1987) associations in two studies and no association in the other (Key et al. 1996). In two small case-control studies of cryptorchidism and maternal 1 st trimester serum testosterone levels, one found a borderline inverse association (Key et al. 1996) and the other found no association (Bernstein et al. 1988).
Cryptorchidism: role of pesticides	(Limited)	Cryptorchidism was associated with paternal occupational exposure to chlorophenate wood

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		preservatives (including an exposure-risk relationship) (Dimich-Ward et al. 1996), parental residence in regions with high agricultural pesticide use (Garcia-Rodriguez et al. 1996), pesticide purchases for field vegetable production and tractor spraying equipment for grain production in a Norwegian farm cohort (Kristensen et al. 1997b), maternal but not paternal occupation in gardening in a large Danish case-control study (Weidner et al. 1998), paternal occupational pesticide exposure (Wang and Wang 2002) and adipose tissue heptachlor epoxide and hexachlorobenzene levels (Hosie et al. 2000). Two studies found non-significant associations between cryptorchidism and adipose tissue DDE (Hosie et al. 2000) or maternal serum DDE levels (Longnecker et al. 2002). Cryptorchidism was not associated with maternal or paternal occupation in farming in the Danish case-control study (Weidner et al. 1998).
Cryptorchidism: role of other environmental toxicants	(Inadequate)	A small case-control study found no association between cryptorchidism and adipose tissue PCB levels (Hosie et al. 2000). Urinary tract birth defects were marginally associated with paternal serum TCDD levels in a study of Vietnam veterans (Wolfe et al. 1995). An ecologic study in Nova Scotia showed no increased risk of genitourinary birth defects in a region with a large hazardous waste site with PAHs, PCBs, benzene, arsenic, lead and other heavy metals (Dodds and Seviour 2001). Boisen et al. (2001) hypothesized that environmental and genetic factors interact periconceptually to disrupt testicular development, causing cryptorchidism and hypospadias in children <i>in utero</i> and reduced semen quality and testicular cancer at older ages.
Hypospadias: role of prenatal maternal hormone therapy	(Inadequate)	Polednak and Janerich (1983) reported a borderline association between hypospadias and maternal 1 st trimester exposure to a hormonal pregnancy test. Calzolari et al. (1986) found an association between hypospadias and prenatal maternal progestin therapy.
Hypospadias: role of pesticides	(Inadequate)	Hypospadias was associated with tractor spraying equipment and grain production in the Norwegian farm cohort study (Kristensen et al. 1997b) but not with maternal or paternal occupation in farming or gardening in a large Danish case-control study (Weidner et al. 1998) or with maternal serum DDE levels in the U.S. Collaborative Perinatal Project (Longnecker et al. 2002).
Hypospadias: role of other environmental toxicants	(Inadequate)	There were borderline or significant associations between hypospadias and maternal residential proximity to a hazardous waste disposal site in a large European case-control study (Dolk et al. 1998) and a UK ecologic study (Elliott et al. 2001).

Health effect	Level of evidence ^a	Comments
Female reproductive tract birth defects	DES Sufficient	Follow-up of the children of pregnant women who participated in a randomized clinical trial of DES showed an increased risk of urogenital birth defects among those exposed during the 1 st trimester (Beral et al. 1981). Three reviews concluded that 1 st trimester maternal DES therapy caused female reproductive tract abnormalities including hypoplastic uterus and cervix, cervical and vaginal adenosis and transverse vaginal ridges (Giusti et al. 1995, Mittendorf 1995, Swan 2000).
Unspecified genitourinary birth defects: role of pesticides	(Inadequate)	There were increased risks of urogenital birth defects among offspring of men employed as licensed pesticide applicators and among offspring of the general Minnesota population living in regions with high corn/soybean or wheat/sugar beet/potato production (Garry et al. 1996). Urinary tract birth defects were associated with pesticide purchases for orchards/greenhouse operations in the Norwegian farm cohort study (Kristensen et al. 1997b) and marginally with paternal serum TCDD levels in a study of Vietnam veterans; serum TCDD is both an important toxicant and a proxy for past phenoxy herbicide exposure (Wolfe et al. 1995).
Puberty: genital development	PCBs and TCDD (Inadequate)	The North Carolina and Michigan birth cohort studies found no association between pubertal stage attainment among adolescents and prenatal or lactational PCB exposure (Gladden et al. 2000, Blanck et al. 2000). A Belgian cross-sectional study of adolescents showed that delayed genital development was associated with current serum PCBs or TCDD-like activity levels in males but not in females (Staessen et al. 2001, Den Hond et al. 2002). The Michigan birth cohort study found associations between <i>accelerated</i> menarche and pubic hair development and maternal serum PBB levels among breastfed but not among non-breastfed daughters (Blanck et al. 2000). A small birth cohort study in the Faroe Islands showed that morning spermaturia, testicular volume and Tanner stages of pubic hair and genital development among boys age 14 yr were not associated with cord tissue PCB levels (Mol et al. 2002).
	Pesticides (Inadequate)	The North Carolina and Michigan birth cohort studies found no association between pubertal stage attainment among adolescents and prenatal or lactational DDE exposure (Gladden et al. 2000, Blanck et al. 2000).
	Lead (Inadequate)	A cross-sectional study of over 2,000 girls NHANES III showed that delayed menarche and pubic hair development were associated with blood lead levels in the range below 10 µg/dL in at two of the three major ethnic subgroups studied (Selevan et al. 2003).

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	Phytoestrogens (Inadequate)	Follow-up at age 20-34 yr of persons randomized at birth to receive soy or cow milk formula showed no associations between average age at menarche and voice change or first ejaculation in boys and exposure to soy formula, a rich source of phytoestrogens (Strom et al. 2001).
Puberty: breast development * based on one large, well-designed study with good control of potential confounders	PCBs and TCDD (Inadequate)	A Belgian cross-sectional study showed an association between delayed breast development in girls and serum TCDD activity but not with serum PCBs (Den Hond et al. 2002). The Michigan birth cohort study showed that breast development was not associated with maternal serum PBB levels among breastfed or non-breastfed daughters (Blanck et al. 2000).
	Lead (Limited*)	A cross-sectional study of over 2,000 girls NHANES III showed that delayed breast development was associated with blood lead levels < 10 µg/dL in at two of the three major ethnic subgroups studied (Selevan et al. 2003).
	Phthalates (Inadequate)	A small case-control study of premature breast development in Puerto Rico showed an association with serum diethyl phthalate levels (Colon et al. 2000).
	Phytoestrogens (Inadequate)	Follow-up at age 20-34 yr of women randomized at birth to receive soy or cow milk formula showed no association between average age at first wearing a bra and exposure to soy formula, a rich source of phytoestrogens (Strom et al. 2001).
Other indicators of reproductive function	(Inadequate)	Follow-up of sons of women who participated in a randomized clinical trial of prenatal DES therapy showed that exposed sons were less likely to be living as married (Beral and Colwell 1981). A cross-sectional study of adolescents showed inverse associations between serum LH and FSH and blood lead levels among boys but not girls with blood lead levels ≥ 10 µg/dL (Vivoli et al. 1993).
Semen quality – role of PCBs, dioxins and related compounds	(Limited)	A fertility clinic-based cross-sectional study showed that sperm motility (but not fertility – see next section) was inversely associated with concentrations of PCB-52, 118, 138 and 153 in semen [note: this is one of the few epidemiologic studies that measured environmental toxicants in semen] (Bush et al. 1986). A review of epidemiologic studies concluded that there was inadequate evidence for associations between semen quality and occupational or background exposure to PCBs (Longnecker et al. 1997). Studies published since this review have shown fairly consistent associations between reduced semen quality and PCB exposure indices. A small study of Yucheng men prenatally exposed to high-levels of PCBs/PCDFs

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		<p>showed that, compared to unexposed men, they had similar sperm counts but more frequent abnormal sperm morphology, reduced sperm motility and reduced ability of sperm to penetrate hamster oocytes <i>in vitro</i> (Guo et al. 2000). One very small study and three larger cross-sectional studies of males in couples with fertility problems all showed inverse associations between sperm motility indices and various serum PCB indices. Among the three larger studies, (i) Dallinga et al. (2002) found an <i>inverse</i> dose-response relationship between progressively motile sperm counts (among men with normal total sperm counts) and blood PCB metabolite levels but <i>positive</i> associations between blood and seminal plasma total PCB levels and one or more semen quality indicators, (ii) Hauser et al. (2003) showed dose-response relationships between reduced sperm motility and abnormal morphology and serum PCB-138 (PCB-138 is a non-TCDD-like PCB congener frequently detected in the general population) but not total, estrogenic or TCDD-like serum PCB levels, (iii) Richthoff et al. (2003) showed an inverse dose-response relationship between sperm motility and PCB-153 levels (also a non-coplanar PCB congener frequently detected in the general population), (iv) there was a <i>positive</i> dose-response relationship between abnormal sperm morphology and serum non-coplanar PCB levels (Dallinga et al. 2002), (v) total sperm counts were not associated with individual or aggregated blood or seminal fluid PCB levels but were inversely associated with blood PCB metabolite levels among the subgroup of men with normal sperm counts (Dallinga et al. 2002). Reviews of toxicology studies (Birnbaum 1995, Brouwer et al. 1995, 1998) concluded that prenatal exposure of experimental animals to relatively low doses of TCDD or TCDD-like organochlorines can cause reduced semen quality. Boisen et al. (2001) hypothesized that environmental and genetic factors interact periconceptually to disrupt testicular development, causing cryptorchidism and hypospadias in children <i>in utero</i> and reduced semen quality and testicular cancer at older ages.</p>
Semen quality – role of pesticides	DBCP, chlordecone Sufficient	A recent review concluded that there is sufficient evidence for associations between reduced semen quality and occupational exposure to dibromochloropropane (DBCP) and chlordecone (Kepone) (Sever et al. 1997). A large cohort study of pesticide applicators working on banana and pineapple plantations and exposed to DBCP showed that 24% had azoospermia (no sperm in semen) (Slutsky et al. 1999).
	Ethylene dibromide Limited	A recent review concluded that there is limited evidence for an association between reduced semen quality and occupational exposure to ethylene dibromide (Sever et al. 1997).

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	TCDD-contaminated phenoxy herbicides Inadequate	A review of epidemiologic studies concluded that there was inadequate evidence for associations between semen quality and occupational or background exposure to TCDD-contaminated phenoxy herbicides (National Academy of Sciences, 2003).
	Other/mixed pesticide exposures (Limited)	A Danish cohort study showed similar changes in total sperm count among pesticide-using and organic farmers during the growing season; the % abnormal sperm heads and an index of abnormal sperm chromatin structure actually decreased among pesticide-using relative to organic farmers (Larsen et al. 1998a). A small cohort of organophosphate production workers in China showed increased sperm chromosomal aneuploidy (Padungtod et al. 1999) and reduced sperm concentration and % motile sperm among exposed compared to unexposed men (Padungtod et al. 2000). A fertility clinic-based case-control study found no association between semen quality and occupational pesticide exposure (Tielemans et al. 1999a). A cohort study of Danish greenhouse workers showed dose-response relationships between reduced sperm concentration and abnormal sperm morphology and estimated dermal pesticide exposure (Abell et al. 2000a). A cross-sectional study showed no association between sperm count or motility and individual or combined blood HCB, DDE or DDT levels (Dallinga et al. 2002). However, a small cross-sectional study of young men in an endemic malaria region with indoor DDT use showed inverse associations between semen volume and total sperm counts and serum DDE levels (Ayotte et al. 2001). A small case-control study of fertile men with below median semen quality parameters showed associations with certain urinary pesticide or pesticide metabolite levels (alachlor, diazinon, atrazine) but not with some other urinary pesticide or pesticide metabolite levels (2,4-D, carbamates, chlorpyrifos) (Swan et al. 2003). A large case-control study based on fertility clinics in The Netherlands showed no association between low semen quality and self-reported pesticide exposure but there were only 12 exposed cases (Tielemans et al. 1999a). A cross-sectional study of men at fertility clinics in Argentina showed associations between low sperm counts and abnormal sperm morphology and self-reported occupational pesticide exposure (Oliva et al. 2001). A similar study in Boston showed no associations between sperm concentrations, motility or abnormal morphology and serum DDE levels (Hauser et al. 2002, Hauser et al. 2003).
Semen quality – role of other toxicants	Solvents (Inadequate)	A fertility clinic-based case-control study showed borderline associations between poor semen quality and occupational exposure to aromatic solvents and urinary solvent metabolite levels; azoospermia was associated with self-reported occupational exposure to aromatic solvents in the subgroup of men who had never fathered a child (Tielemans et al. 1999a). Another fertility

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		clinic-based study showed borderline or significant associations between occupational solvent exposure and reduced sperm counts and abnormal sperm morphology (Oliva et al. 2001).
	Phthalates (Inadequate)	A fertility clinic-based study in Boston showed borderline or significant dose-response relationships between low sperm concentration, reduced sperm motility, abnormal sperm morphology and urinary metabolite levels of dibutyl and dibenzyl phthalates (Duty et al. 2003a); this study also showed an association between sperm DNA strand breaks and urinary metabolite levels of diethyl phthalate (2003b).
	Metals (Inadequate)	There were no associations between semen quality and self-reported occupational exposure to welding fumes or urinary manganese, cadmium, chromium or nickel levels (Tielemans et al. 1999a).
	Outdoor air pollution (Inadequate)	A small cross-sectional study showed an association between exposure to medium or high outdoor air pollution during the 90 days before semen collection and abnormal sperm morphology and chromatin structure but not with sperm concentration or count (Selevan et al. 2000).
Semen quality – role of therapeutic hormones	Inadequate	Two reviews of studies on long-term health effects of DES concluded that there was limited and inconsistent evidence for an association between prenatal maternal DES therapy and reduced semen quality in exposed sons (Giusti et al. 1995, Swan 2000).
Semen quality – role of dietary phytoestrogens	(Inadequate)	A small (14 men) controlled exposure study showed no change in semen quality parameters after consumption of soy extract tablets (40 mg of genestein, daidzein and glycitein daily for 2 months) (Mitchell et al. 2001).
Male fertility – role of PCBs, dioxins and related compounds	(Inadequate)	A fertility clinic-based study reported that male fertility status was not associated with semen PCB levels (stated without presenting data in paper) (Bush et al. 1986). Two Michigan cohort study of families that consume Great Lakes fish (contaminated with PCBs and other organochlorine compounds) showed that conception delay was associated with male but not with female partner sports-caught fish consumption (Courval et al. 1999). In contrast, the New York Angler Cohort Study found associations between conception delay and female but not male partner sports-caught fish consumption (Buck et al. 1999, 2000); conception delay was not associated with estimated PCB intake by male or female partners (Buck et al. 2000, 2002).

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Male fertility – role of pesticides	(Inadequate)	A fertility clinic-based study reported that male fertility status was not associated with semen DDE, hexachlorobenzene or mirex levels (stated without presenting data in paper) (Bush et al. 1986). A cross-sectional study of male Danish and French agricultural workers showed no associations between self-reported time to pregnancy and exposure to farm, greenhouse or vineyard pesticides (Thonneau et al. 1999a, 1999b). A retrospective cohort study of Ontario farm families showed no association between self-reported time to pregnancy and male partner's pesticide use (Curtis et al. 1999).
Male fertility – role of other toxicants	(Inadequate)	A cohort study in Belgium showed that reduced male fertility was associated with occupational exposure to airborne manganese salts but not with metallic mercury vapour exposure (Lauwerys et al. 1985). A Finnish cohort study found an association between fertility and male partner blood lead level; among the subgroup of couples with at least one previous pregnancy, the likelihood of conception was not associated with male partner blood lead level (Sallmen et al. 2000). A cross-sectional study of couples seeking <i>in vitro</i> fertilization showed that <i>in vitro</i> fertilization success was not associated with male partner occupational exposure to welding fumes or organic solvents (Tielemans et al. 1999b). A cross-sectional study of men working in plants producing or using di(2-ethylhexyl)phthalate showed no associations between time to pregnancy and exposure level during the previous 3 months (Modigh et al. 2002).
Male fertility – role of prenatal maternal DES therapy	(Inadequate)	Follow-up of men whose mothers participated in a randomized clinical trial of prenatal DES therapy showed similar fertility among exposed and unexposed men (Wilcox et al. 1995). The latter review concluded that there was limited and inconsistent evidence of reduced fertility among exposed sons (Swan 2000).
Female fertility	PCBs (Inadequate)	Two Michigan cohort study of families that consume Great Lakes fish (contaminated with PCBs and other organochlorine compounds) showed that conception delay was associated with male but not with female partner sports-caught fish consumption (Courval et al. 1999). In contrast, the New York Angler Cohort Study found associations between conception delay and female but not male partner sports-caught fish consumption (Buck et al. 1999, 2000). This study found that conception delay was not associated with estimated PCB intake by male or female partners (Buck et al. 2000, 2002). A recent report of this study (based on women trying to conceive and closely monitored with the aid of home pregnancy test kits) showed that PCBs-205 and 206 were associated with conception delay while PCBs-19, 48 and 169 were associated

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		with increased likelihood of conception (Buck et al. 2002). Unlike the earlier report of this study, the recent report showed no association between conception delay and female partner sports-caught fish consumption. Follow-up of women poisoned at age 15-44yr by PCBs during the Yucheng incident and a comparison group showed similar fertility rates in the two groups and no association between fertility problems and baseline serum PCB levels (Yu et al. 2000).
	Pesticides (Limited)	A retrospective cohort study of Ontario farm families showed borderline associations between self-reported time to pregnancy and female partner's pesticide use including dicamba, 2,4-D and organophosphates (Curtis et al. 1999). A cohort study of couples Danish female greenhouse workers showed associations between delayed conception and self-reported occupational handling of plant cultures, handling of plant cultures without gloves and pesticide spraying (Abell et al. 2000b).
	Solvents (Inadequate)	A case-control study showed that female infertility was associated with self-reported occupational solvent exposure (Smith et al. 1997).
	Prenatal maternal DES therapy Limited	Two reviews of literature on long-term health effects of prenatal DES exposure concluded that exposed daughters had increased risks of menstrual irregularity, primary infertility, ectopic pregnancy, early fetal death and preterm birth (Giusti et al. 1995, Swan 2000).
Testicular cancer – role of pesticides	Mixed exposures (Limited)	Cohort studies of licensed pesticide applicators in Sweden and Florida showed increased risks of testicular cancer in (Wiklund et al. 1989, Fleming et al. 1999). A population-based case-control study in Ontario found no association with self-reported occupations potentially exposed to pesticides (Knight et al. 1996). Two case-control studies and a US cohort study (98% were farmers) showed that testicular cancer was not associated with occupation as farmers (Van den Eeden et al. 1991, Moller 1997, Fleming et al. 2003). The latter study had limited ability to assess the risk of testicular cancer stated this finding without providing data. Testicular cancer was not associated with maternal employment in agriculture (Moller 1997). A Norwegian farm cohort study showed an increased risk of testicular cancer compared to the general population with a higher risk among those age 15-19 years compared to older men but there was no association with agricultural pesticide purchases (Kristensen et al. 1996a). A Swedish case-control study showed associations between testicular cancer and insect repellent use and occupations in farming (Hardell et al. 1998, Ohlson and Hardell 2000).

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	TCDD-contaminated phenoxy herbicides Inadequate	A case-control study of US veterans showed no association between testicular cancer and exposure to Agent Orange (a 50:50 mix of the phenoxy herbicides 2,4-D and 2,4,5-T) (Bullman et al. 1994). A recent review concluded that there is insufficient evidence for an association between testicular cancer and phenoxy herbicide exposure (National Academy of Sciences 2003).
	DDT/DDE (Inadequate)	An ecologic study of US state-level testicular cancer mortality rates showed no association with estimated state-level DDT use (Cocco and Benichou 1998); note that testicular cancer survival rates are quite high and mortality rates reflect both the combined risks of developing disease and experiencing treatment failure. A recent small case-control study showed that testicular cancer was marginally associated with the subjects' plasma DDE levels (Hardell et al. 2003).
	Other specific pesticides (Inadequate)	An ecologic study in California showed that testicular cancer incidence among Hispanic males was marginally associated with county-level atrazine use but was inversely associated with use of captan or diazinon (Mills 1998). A recent small case-control study showed that testicular cancer was marginally associated with the subjects' plasma hexachlorobenzene and more strongly associated with their mothers' plasma hexachlorobenzene levels; the latter relationship was especially strong among the subset of non-seminoma testicular cancers (Hardell et al. 2003).
Testicular cancer – role of other toxicants	(Inadequate)	A Swedish case-control study showed an association between testicular cancer and occupation as plastics workers (Hardell et al. 1997, Hardell et al. 1998, Ohlson and Hardell 2000). A case-control study of germ cell tumours (about 60% in ovaries or testicles and 40% at other sites) showed associations with maternal and paternal occupational exposure to plastic or resin fumes (Shu et al. 1995). A hospital-based case control study showed an association between non-seminoma testicular cancer and dietary fat (Sigurdson et al. 1999); although speculative, dietary fat may be acting as a proxy for intake of fat-soluble toxicants such as PCBs and dioxins.
Testicular cancer – role of prenatal maternal hormone therapy	(Limited)	Testicular cancer was associated with maternal 1 st trimester exogenous hormone therapy (DES, estrogen, progestin or hormonal pregnancy test) in a relatively small case-control study (Depue et al. 1983) but a larger study found no relationship (Moss et al. 1986). Two literature reviews concluded that there was limited and inconsistent evidence for an association between testicular cancer and maternal prenatal DES therapy (Giusti et al. 1995, Swan 2000). Since these reviews, a large population-based case-control study in Ontario (Weir et al. 2000) showed a

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		moderately strong association between testicular cancer and prenatal maternal exogenous hormone therapy and a cohort study in the USA (Strohsnitter et al. 2001) found a borderline association with prenatal maternal DES therapy but was limited by low statistical power.
Testicular cancer – role of host factors	Age at puberty (Limited)	Five case-control studies have shown associations between early onset of puberty and testicular cancer (Moss et al. 1986, Gallagher et al. 1995, Moller and Skakkebaek 1996, Weir et al. 1998, Coupland et al. 1999).
	Cryptorchidism (Sufficient)	Several case-control studies have shown convincing evidence of an association between testicular cancer and cryptorchidism (Schottenfeld et al. 1980, Depue et al. 1983, Moss et al. 1986, Brown et al. 1987, Gallagher et al. 1995, Prener et al. 1996), Davies et al. 1996, Coupland et al. 1999, Weir et al. 2000). There is conflicting evidence as to whether or not the risk of testicular cancer in unilateral cryptorchidism is elevated in both the normal and the undescended testicle, cancer (Schottenfeld et al. 1980, Prener et al. 1996).
Cervicovaginal clear-cell adenocarcinomas of the vagina and cervix – role of prenatal maternal DES therapy	Sufficient	Two reviews concluded that DES therapy of pregnant women caused cervicovaginal clear-cell adenocarcinomas of the vagina and cervix among prenatally exposed daughters with the risk being greatest for those exposed during the 1 st trimester (Giusti et al. 1995, Mittendorf 1995).
Thyroid function – role of PCBs, dioxins and related compounds: epidemiologic studies	Reduced maternal plasma TT3 and TT4 Limited Reduced maternal plasma FT4 (Inadequate) Increased maternal plasma TSH (Inadequate)	Dutch birth cohort studies showed inverse dose-response relationships between prenatal and postnatal maternal plasma TT3 and TT4 levels and breast milk PCB, PCB-TEQ and total dioxin-TEQ levels; maternal plasma FT4 and TSH levels were not associated with breast milk PCB- or total dioxin-TEQ levels (Koopman-Esseboom et al. 1994, Sauer et al. 1994). Longnecker et al. (1997) concluded that there is limited epidemiologic evidence for associations between reduced maternal T3 and T4 levels and background prenatal PCB exposures.
	Reduced neonatal plasma TT4	Breast milk PCB- and total dioxin-TEQ levels were associated with reduced neonatal plasma FT4 and TT4 levels and increased neonatal plasma TSH levels in the larger Dutch study (Sauer

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	(Inadequate) Reduced neonatal plasma FT4 (Inadequate) Increased neonatal plasma TSH (Inadequate)	et al. 1994) but the North Carolina birth cohort study found no associations between cord serum TT4, FT4 or TSH levels and breast milk PCB levels (Longnecker et al. 2000). A Faroe Islands birth cohort study found an inverse association between cord blood FT3 and cord serum PCB levels (Steuerwald et al. 2000). A small study of neonates in northern and southern Quebec showed that cord plasma TT3 and FT4 levels were associated with cord plasma pentachlorophenol levels and with the sum of cord plasma pentachlorophenol and hydroxylated PCB levels but not with cord plasma levels of individual or total PCB congeners or total hydroxylated PCBs; neonatal cord plasma TSH levels were <i>inversely</i> associated with cord plasma PCB and OH-PCB levels (Sandau et al. 2002). Longnecker et al. (1997) concluded that there is limited epidemiologic evidence for associations between increased infant TSH levels and background prenatal PCB exposures and there is inadequate evidence for an association between infant plasma TSH levels and prenatal dioxin exposure.
	Reduced childhood plasma FT3 (Inadequate) Increased childhood plasma TSH (Inadequate)	A cross-sectional study of children age 7-10 yr living in PCB-contaminated regions in Germany showed that serum FT3 levels were inversely associated with blood levels of individual PCBs (138, 153, 180, 183 and 187) and the total of the 7 PCB congeners measured; serum TSH levels were associated with blood PCB-118 (a dioxin-like congener) levels but not the sum of the 7 PCBs (Osius et al. 1999). A cross-sectional study of older children (age 17 yr) in Slovakia showed similar prevalence rates of elevated serum TSH levels but a higher average thyroid volume among those living in PCB-contaminated compared to unexposed regions (this study did not measure blood PCB levels) (Langer et al. 1998).
Thyroid function – role of PCBs, dioxins and related compounds: experimental studies		Cheek et al. (1999) found that hydroxylated PCB metabolites bound to human transthyretin <i>in vitro</i> with affinities similar to or greater than T4 and to human thyroid receptor and thyroid-binding globulin but with much lower affinities than T3 or T4. The latter study concluded that PCBs and their hydroxylated metabolites alter thyroid function mainly by competing for transthyretin, thereby increasing hepatic T4 metabolism. Other reviewers concluded that (i) prenatal and lactational exposure to PCBs, PCDDs or PCDFs can cause reduced thyroid hormone levels in experimental animals, (ii) early gestational exposure of rodents to PCBs caused severely reduced fetal and neonatal brain T4 levels, (iii) neurotoxic effects of PCBs and dioxins may involve multiple mechanisms including the Ah receptor and interference with thyroid function and, (iv) many PCBs and dioxins have structural similarities to T3 and T4 (Brouwer et al. 1995, Brouwer et al. 1998, Porterfield 2000).

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Thyroid function – role of pesticides	Pentachlorophenol (Inadequate)	A study of neonates in northern Canada showed inverse associations between cord plasma FT4, T3 and thyroid binding globulin and cord plasma pentachlorophenol levels (Sandau et al. 2002).
	DDT, β -HCH (Inadequate)	A cross-sectional study of neonates in Spain showed associations between neonatal plasma TSH and cord serum DDE and β -hexachlorocyclohexane levels but not with cord serum hexachlorobenzene levels (Ribas-Fito et al. 2003).
Thyroid function – metals (lead, mercury, cadmium)	(Inadequate)	A cross-sectional study of children age 7-10 yr living in PCB-contaminated regions in Germany showed that serum thyroid hormone levels were not associated with blood lead or urinary mercury levels but blood cadmium was associated with decreased FT4 and increased TSH levels (Osius et al. 1999).

2. Reproductive tract birth defects

Reference, location	Design	Exposure	Results	Association ^a	DR ^b	Covariates
(Beral and Colwell 1981), UK	Randomized clinical trial, 161 diabetic pregnant women; long-term follow-up of 70 exposed and 66 unexposed children	DES and ethisterone therapy during pregnancy	Risk of urogenital birth defects higher among exposed infants; risk confined to those exposed before gestation wk 13 (prevalence rates, exposed vs unexposed infants)	14 vs 9%		
(Polednak and Janerich 1983), Upstate New York	Case-control study, 99 cases hypospadias, 99 live birth controls matched for maternal age and race	Mother-reported exposure information; 7 case and 2 control mothers received 1 st trimester hormone pregnancy tests; 5 case and 10 control mothers received “supportive hormone” therapy during the 1 st trimester	Borderline association between hypospadias and maternal 1 st trimester pregnancy test (odds ratio)	3.5 (0.05 < p < 0.1)		Matched pairs analysis
			Hypospadias not associated with 1 st trimester “supportive hormone” therapy (odds ratio for exposure during 2 nd month of gestation, 4 case mothers exposed)	0.4 (p > 0.05)		
(Beard et al. 1984), Rochester,	Population-based case-control study, 113 cases cryptorchidism born during	9 case (and 31 control) mothers received 1 st trimester estrogen therapy including steroidal	Cryptorchidism not associated with maternal 1 st trimester estrogen therapy	1.9 (CI 0.5-6.6)		Previous abortion, infertility, toxemia, bleeding,

^a Entries in this column include odds ratios, relative risks and certain other statistical measures of association as published in original epidemiologic studies; an entry of ‘+’ means the measure of association was not an odds ratio or relative risk and was statistically significant at the 0.05 level; an entry of ‘(+)’ means the association was almost statistically significant.

^b ‘DR’ refers to a dose-response relationship in an epidemiologic study; an entry of ‘+’ means the measure of dose-response relationship used in the citation was statistically significant at the 0.05 level; an entry of ‘(+)’ means the association was almost statistically significant.

Minnesota	1943-1973, 226 live birth community controls (I) matched for YOB, maternal age, parity, gravidity and 226 live birth controls (II) matched for hospital-of-birth and YOB; assessed maternal prenatal estrogen therapy	estrogen (5), non-steroidal estrogen (2) and non-steroidal estrogen/progestin (2)	(odds ratios using control groups I and II)	1.4 (CI 0.4-4.5)	spontaneous onset of labour, breech vaginal delivery, smoking, gestational age, prenatal progestin use
			Cryptorchidism not associated with maternal prenatal progestin therapy (odds ratios using control groups I and II)	0.9 (CI 0.3-3.3) 0.7 (CI 0.2-2.3)	As above but including prenatal estrogen
(Depue 1984), Collaborative Perinatal Project, USA	Case-control study within the 1958-1965 Collaborative Perinatal Project, 300 cases cryptorchidism, 599 matched controls	Mother-reported exposures; 2 case/1 control mothers received prenatal estradiol therapy and 5 case/4 control mothers received prenatal DES therapy; 10 case/19 control mothers received prenatal progestin therapy	Borderline association between cryptorchidism and maternal prenatal estrogen therapy	2.8 (CI 0.9-8.8)	Matched for race; results not influenced by maternal age, parity, age at menarche, infertility, previous fetal death, diabetes, prenatal infections/fever
			Cryptorchidism not associated with maternal prenatal progestin therapy	1.0 (CI 0.5-2.2)	As above
			3/300 case mothers and 10/599 control mothers took oral contraceptives during first 2 mos of gestation (crude odds ratio)	0.6	
(Calzolari et al. 1986), Italy	Case-control study, 168 cases hypospadias, 378 live birth controls; assessed	Mother-reported exposure information; 51 case and 82 control mothers received	Hypospadias associated with prenatal progestin therapy (prevalence, case vs control)	32 vs 22% (p < 0.05)	

	progestin use for threatened or previous early fetal death	prenatal progestin therapy;	mothers)		
(Burton et al. 1987), UK	Hospital-based case-control study, 19 cases cryptorchidism, 22 controls	Measured maternal estradiol levels during 1 st trimester	Borderline association between cryptorchidism and <i>reduced</i> prenatal maternal estradiol level (difference between case and control mothers)	-2.7 pM/L (CI -6.3 to 0.9)	
(Bernstein et al. 1988), Collaborative Perinatal Study, USA	Case-control study within 1958-1965 Collaborative Perinatal Project, 25 cases cryptorchidism, 25 matched controls; assessed maternal hormone levels during early pregnancy	Measured 1 st trimester maternal serum estradiol, human chorionic gonadotrophin (HCG), total and free testosterone and sex-hormone binding globulin (SHBG)	Borderline association between cryptorchidism and 1 st trimester maternal serum free estradiol level (cases vs controls)	11.0 vs 9.5 ng/dL (p = 0.07)	Matched for center and maternal age, parity, weight and gestation length
			Cryptorchidism not associated with 1 st trimester maternal serum free testosterone levels (cases vs controls)	3.4 vs 3.6 ng/dL (p = 0.22)	
			Cryptorchidism not associated with 1 st trimester maternal total serum estradiol, HCG, total or free testosterone or SHBG levels		
(McBride et al. 1991), Vancouver, Canada	Population-based case-control study, 244 cryptorchidism cases persistent or treated by age 1 yr, 488 controls matched for birth date within 6 mos; substudy of 103 cases and 128 healthy male sibling	Mother-reported exposure information; 9 case and 15 control mothers took oral contraceptive hormones within 1 month of conception	Cryptorchidism not associated with preconceptual oral contraceptive use (odds ratio for use < 1 month before vs unexposed); similar results using sibling controls	0.9 (p > 0.05)	

controls					
(Giusti et al. 1995), USA	Review of literature on long-term health effects of prenatal DES exposure ^c	Prenatal maternal DES therapy	Daughters: T-shaped and hypoplastic uteri, cervicovaginal ridges		
			Sons: Limited and inconsistent evidence of epididymal cysts, hypotrophic testicles and cryptorchidism		
(Mittendorf 1995), Chicago	Review of literature on carcinogenic and teratogenic effects of prenatal DES exposure	Mothers prenatally exposed to DES therapy	Daughters: cervical ectropion, cervical and vaginal adenosis and gross abnormalities including transverse vaginal ridges, cervical collars and hoods, cervical hypoplasia, small-volume endometrial cavities (the latter were found in more than half of exposed daughters)		
(Wolfe et al. 1995), USA	Cross-sectional study, Vietnam veterans and wives/partners; 1006 conceptions among exposed men and 1235 among unexposed comparison group with known serum TCDD levels; assessed birth	Aerial spraying of Agent Orange during 1962-71, see Wolfe et al. 1995 above	Borderline association between urinary tract birth defects and paternal serum TCDD levels (relative risk, high vs background) (only 7 case fathers had high exposure)	2.1 (CI 0.8-5)	Paternal race, maternal prenatal smoking, prenatal alcohol, parent's ages, paternal military occupation in Southeast Asia

^c Although DES was a medical drug and not an environmental contaminant, it is included here to show the potential health effects of prenatal exposure to a potent hormone.

	defects – 177 among infants of potentially exposed fathers, 204 among infants of comparison fathers				
(Garcia-Rodriguez et al. 1996), Spain	Hospital-based case-control study, 131 cases of cryptorchidism, 243 other diagnoses, age 1-16 yr, residing in 15 health care districts	Pesticide exposure of cases and controls was inferred from residence in health care districts categorized by an agricultural pesticide-use intensity index	Borderline association between cryptorchidism and ecologic pesticide exposure index (odds ratio, highest vs lowest exposure region)	2.5 (CI 0.9-7.3)	Age, health care district population
(Key et al. 1996), Oxford, UK	Case-control study within birth cohort of 7,500 boys, 28 cases cryptorchidism (persistent from birth to age 3 mos), 108 controls; cases identified by trained nurse examinations at birth and reexamination of cases at age 3 mos; assessed maternal hormone levels during early pregnancy	Measured maternal serum hormone levels during gestation wk 6-20	Non-significantly higher maternal serum estradiol levels among case mothers during gestation wk 15-20 (cases vs controls); avg serum estradiol levels during gestation wk 6-14 almost identical in case and control mothers	17.5 vs 13.6 nM/L (p = 0.14)	Birth weight, gestation week
			Borderline lower maternal serum testosterone levels among case mothers during gestation wk 6-14 (cases vs controls); avg serum testosterone levels during gestation wk 15-20 slightly higher among case mothers	3.7 vs 5.0 nM/L (p = 0.06)	Birth weight
(Garry et al. 1996), Minnesota	Cohort and ecologic studies, 34,772 pesticide applicators; linked state birth and birth defect	Occupation as certified applicators of restricted-use pesticides	Increased risk of urogenital birth defects among pesticide applicators (odds ratio, applicators vs general	1.7 (CI 1.1-2.6)	Maternal age

	registry records; 20 urogenital birth defects among offspring of pesticide applicators; also assessed birth defect rates in general population by agricultural region		population)			
		Ecologic exposure index for each of 25 regions based on statewide pesticide and crop production survey	Increased risks of urogenital birth defects in general population living in regions with corn/soybean or wheat/sugar beet/potato crops	+		Maternal age
(Dimich-Ward et al. 1996), British Columbia	Nested case-control study within cohort of 19675 offspring of 9512 men exposed for at least one yr in a sawmill using chlorophenate wood preservatives, 105 genital organ birth defects; linked cohort and health outcome databases; 5 controls per case	Father's exposure to chlorophenate wood preservatives estimated from job titles and duration of employment in each job; chlorophenate wood preservatives known to be contaminated with PCDDs including TCDD	Cryptorchidism was associated with paternal occupational chlorophenate exposure (odds ratio as above) (number of highly exposed case fathers not stated)	1.4 (CI 1.0-1.9)	+	Sex, parental ages
(Kristensen et al. 1997), Norway	Cohort study, linked birth registry and five agricultural and horticultural censuses; 192,417 births of farmers (1967-91); comparison group of 61,351 births to non-farmers in agricultural municipalities; 245 cryptorchidism cases, 270 hypospadias cases	Expenditures on pesticides, possession of tractor pesticide spraying equipment (based on census closest to time of birth)	Borderline decreased risk of cryptorchidism among farm births	0.8 (CI 0.6-1.0)		Year of birth, maternal age, geographic region, parental consanguinity
			Cryptorchidism associated	2.3		As above

			with pesticide purchase for field vegetable production	(CI 1.3-4.0)	
			Borderline association between hypospadias and tractor spraying equipment for grain production	1.5 (CI 1.0-2.3)	As above
(Weidner et al. 1998), Denmark	Country-wide case-control study, 6,177 cases cryptorchidism, 1,345 cases hypospadias, 23,273 healthy live birth controls; linked national health and tax records	Assessed parental occupation in farming or gardening industry as recorded on tax records for year of conception	Cryptorchidism associated with maternal occupation in gardening	1.7 (CI 1.1-2.5)	Year of birth, birth weight
			Cryptorchidism not associated with maternal occupation in farming or with paternal occupation in either farming or gardening		As above
			Hypospadias not associated with maternal or paternal occupation in farming or gardening		As above
(Dolk et al. 1998), Belgium, Denmark, France, Italy, UK	Population-based case-control study, 1,089 birth defect cases, 2,366 controls, mothers resided within 7 km of a hazardous waste landfill site	Assessed residential proximity to 21 hazardous waste landfill sites	Borderline association between hypospadias and residence < 3 km of a landfill site	2.0 (CI 1.0-3.9)	Maternal age, SES
(Hosie et al. 2000), Germany	Case-control study of cryptorchidism, 18 cases, 30 controls	Measured DDT/DDE, PCBs (6 congeners), toxaphenes, hexachlorocyclohexane, chlorinated cyclodienes and	Cryptorchidism not associated with adipose tissue PCB levels (median levels in cases and controls)	561 vs 558 ng/g lipid (p > 0.05)	

chlorinated benzenes in adipose tissue samples					
			Cryptorchidism associated with higher adipose tissue heptachlor-epoxide and hexachlorobenzene levels (respective median levels in cases and controls)	5.2 vs 2.4 ng/g lipid (p< 0.05) 61 vs 20 ng/g lipid (p< 0.05)	
			Non-significant association between cryptorchidism and adipose tissue DDT/DDE levels (median levels in cases and controls)	341 vs 195 ng/g lipid (NS)	
(Swan 2000), USA	Review of literature on long-term effects of prenatal DES exposure	Prenatal maternal exposure to DES therapy	Vaginal adenosis more prevalent at autopsy of stillbirths and neonatal deaths among DES-exposed compared to unexposed daughters (70 vs 4%)		
			DES-exposed sons had increased risk of genital tract abnormalities including epididymal cysts, hypotrophic testicles, cryptorchidism, hypoplastic penis, hypospadias		
(Dodds and Seviour 2001), Nova Scotia, Canada	Ecologic study, Sydney (region of former steel production and location of a large hazardous waste site); assessed pregnancy outcomes in Sydney, the	Maternal residence in Sydney at time of delivery; contaminants in waste site include PAHs, PCBs, benzene, arsenic, lead, other heavy metals	Risk of genitourinary birth defects not elevated in Sydney relative to remainder of province (relative risk)	1.2 (CI 0.7-2.2)	Major anomaly, maternal age, smoking, parity

	rest of Cape Breton County and the rest of Nova Scotia				
(Boisen et al. 2001), Denmark	Review of literature and hypothesis for a testicular dysgenesis syndrome	Poor Leydig cell and Sertoli cell function, respectively, cause androgen insufficiency and impaired germ cell differentiation <i>in utero</i>	Environmental and genetic factors interact periconceptually to disrupt testicular development and cause cryptorchidism and hypospadias <i>in utero</i> and reduced semen quality and testicular cancer later		
(Elliott et al. 2001), UK	Ecologic study, birth defects and low birth weight, UK 1982-1997; over 8 million live births, 43,471 late fetal deaths, 124,597 birth defects	Maternal residence within 2 km of any of 9,565 landfill sites operational during 1982-1997; included 774 hazardous waste sites	Hypospadias associated with maternal residence near hazardous waste sites	1.11 (CI 1.03-1.21)	Low income
(Longnecker et al. 2002), Collaborative Perinatal Project, USA	Nested case-control study, 219 cases cryptorchidism, 199 cases hypospadias, 167 cases polythelia, 552 healthy controls; infants of pregnant women recruited during 1959-1966	Measured DDE levels in stored maternal serum samples; median DDE levels in mothers of cryptorchidism, hypospadias and polythelia cases and controls, respectively, were 4.3, 4.2, 6.3 and 4.2 µg/g lipid	Non-significant association between cryptorchidism and maternal serum DDE levels (odds ratio, maternal serum DDE ≥ 60 vs < 15 µg/L)	1.4 (CI 0.8-2.6)	Race, serum triglyceride and cholesterol levels
			No association between hypospadias and maternal serum DDE levels (odds ratio, maternal serum DDE ≥ 60 vs < 15 µg/L)	1.3 (CI 0.6-2.5)	As above
(Wang and Wang 2002), China	Hospital-based case-control study, 99 cases cryptorchidism, 2 matched controls per case	Parent-reported information on prenatal exposures	Cryptorchidism associated with paternal occupational pesticide exposure	13 (CI 2.9 - 56)	

Cryptorchidism: summary

Prenatal maternal hormone therapy: DES

Follow-up of the children of pregnant women who participated in a randomized clinical trial of DES showed an increased risk of urogenital birth defects among those exposed during the 1st trimester (Beral et al. 1981). Three reviews concluded that 1st trimester maternal DES therapy caused male reproductive tract abnormalities including cryptorchidism, hypospadias, epididymal cysts and hypotrophic testicles and penis (Giusti et al. 1995, Mittendorf 1995, Swan 2000).

Prenatal maternal hormone therapy: estradiol, oral contraceptive hormones, progestins

Two case-control studies of cryptorchidism found borderline (Depue 1984) or non-significant associations with prenatal estradiol or DES therapy (Beard et al. 1984); both studies showed no relationship with prenatal maternal progestin therapy. Depue et al. (1984) and McBride et al. (1991) found no association between cryptorchidism and maternal oral contraceptive use during early gestation but both studies had low statistical power for testing this association.

Endogenous maternal hormones: serum estradiol or testosterone

Among three case-control studies of cryptorchidism and maternal 1st trimester endogenous serum estradiol levels, there were borderline positive (Bernstein et al. 1988) and inverse (Burton et al. 1987) associations in two studies and no association in the other (Key et al. 1996). In two small case-control studies of cryptorchidism and maternal 1st trimester serum testosterone levels, one found a borderline inverse association (Key et al. 1996) and the other found no association (Bernstein et al. 1988).

Pesticides

Cryptorchidism was associated with paternal occupational exposure to chlorophenate wood preservatives (including an exposure-risk relationship) (Dimich-Ward et al. 1996), parental residence in regions with high agricultural pesticide use (Garcia-Rodriguez et al. 1996), pesticide purchases for field vegetable production and tractor spraying equipment for grain production in a Norwegian farm cohort (Kristensen et al. 1997b), maternal but not paternal occupation in gardening in a large Danish case-control study (Weidner et al. 1998), paternal occupational pesticide exposure (Wang and Wang 2002) and adipose tissue heptachlor epoxide and hexachlorobenzene levels (Hosie et al. 2000). Two studies found non-significant associations between cryptorchidism and adipose tissue DDE (Hosie et al. 2000) or maternal serum DDE levels (Longnecker et al. 2002). Cryptorchidism was not associated with maternal or paternal occupation in farming in the Danish case-control study (Weidner et al. 1998).

Other environmental toxicants

A small case-control study found no association between cryptorchidism and adipose tissue PCB levels (Hosie et al. 2000). Urinary tract birth defects were marginally associated with paternal serum TCDD levels in a study of Vietnam veterans (Wolfe et al. 1995). An ecologic study in Nova Scotia showed no increased risk of genitourinary birth defects in a region with a large hazardous waste site with PAHs, PCBs, benzene, arsenic, lead and other heavy metals (Dodds and Seviour 2001). Boisen et al. (2001) hypothesized that environmental and genetic factors interact periconceptually to disrupt testicular development, causing cryptorchidism and hypospadias in children *in utero* and reduced semen quality and testicular cancer at older ages.

Hypospadias

Prenatal hormone therapy

Polednak and Janerich (1983) reported a borderline association between hypospadias and maternal 1st trimester exposure to a hormonal pregnancy test. Calzolari et al. (1986) found an association between hypospadias and prenatal maternal progestin therapy.

Pesticides

Hypospadias was associated with tractor spraying equipment and grain production in the Norwegian farm cohort study (Kristensen et al. 1997b) but not with maternal or paternal occupation in farming or gardening in a large Danish case-control study (Weidner et al. 1998) or with maternal serum DDE levels in the U.S. Collaborative Perinatal Project (Longnecker et al. 2002).

Other environmental toxicants

There were borderline or significant associations between hypospadias and maternal residential proximity to a hazardous waste disposal site in a large European case-control study (Dolk et al. 1998) and a UK ecologic study (Elliott et al. 2001).

Female reproductive tract birth defects

Follow-up of the children of pregnant women who participated in a randomized clinical trial of DES showed an increased risk of urogenital birth defects among those exposed during the 1st trimester (Beral et al. 1981). Three reviews concluded that 1st trimester maternal DES therapy caused female reproductive tract abnormalities including hypoplastic uterus and cervix, cervical and vaginal adenosis and transverse vaginal ridges (Giusti et al. 1995, Mittendorf 1995, Swan 2000).

Unspecified urogenital birth defects

There were increased risks of urogenital birth defects among offspring of men employed as licensed pesticide applicators and among offspring of the general Minnesota population living in regions with high corn/soybean or wheat/sugar beet/potato production (Garry et al. 1996). Urinary tract birth defects were associated with pesticide purchases for orchards/greenhouse operations in the Norwegian farm cohort study (Kristensen et al. 1997b) and marginally with paternal serum TCDD levels in a study of Vietnam veterans; serum TCDD is both an important toxicant and a proxy for past phenoxy herbicide exposure (Wolfe et al. 1995).

3. Pubertal development and related outcomes

Reference, location	Design	Exposure	Results	Association ^d	DR ^e	Covariates
(Beral and Colwell 1981), UK	Randomized clinical trial, 161 diabetic pregnant women; long-term follow-up of 70 exposed and 66 unexposed children	DES and ethisterone therapy during pregnancy	Proportion of sons living as married lower among those exposed to DES before gestation wk 13 compared to non-exposed sons	3/16 vs 13/21 (p < 0.01)		
(Vivoli et al. 1993), Trento, Italy	Cross-sectional study, 418 children age 11-13 yr; measured serum hormones (LH, FSH, T, E2, dehydroepiandrosterone sulfate)	Mean blood lead levels in boys and girls were 8.5 and 7.0 µg/dL (range 1.5-17.5 µg/dL)	Serum LH and FSH levels not associated with blood lead levels among boys or girls (range of linear regression coefficients)	-0.10 to 0.03 (p > 0.1)		
			Among boy with blood lead levels ≥ 10 µg/dL, serum LH and FSH levels were inversely associated with blood lead levels (respective linear regression coefficients)	-0.43 (p = 0.002)		
				-0.36 (p = 0.01)		
			Borderline inverse association between serum estradiol and blood lead levels in females (linear regression coefficient)	-0.13 (p = 0.08)		
			Borderline inverse association between serum dehydroepiandrosterone and	-0.13 (p = 0.07)	(+)	

^d Entries in this column include odds ratios, relative risks and certain other statistical measures of association as published in original epidemiologic studies; an entry of '+' means the measure of association was not an odds ratio or relative risk and was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

^e 'DR' refers to a dose-response relationship in an epidemiologic study; an entry of '+' means the measure of dose-response relationship used in the citation was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

			blood lead levels in males and females (respective linear regression coefficients)	-0.13 (p = 0.06)	
			Serum testosterone not associated with blood lead in boys (linear regression coefficient)	0.02 (p = 0.8)	
(Gladden et al. 2000), North Carolina	Birth cohort study, 594 children; assessed pubertal growth and development using self-reported height, weight and Tanner stage of pubertal development	Measured breast milk, maternal blood, cord blood and placental PCB and DDE levels; assessed average (of all measurements) and lactational exposures	Age at menarche not associated with prenatal or lactational PCB exposure categories (avg age for highest vs lowest PCB category) (p for trend = 0.46 and 0.69)	Prenatal 12.6/12.7 yr Lactational 12.8/12.8 yr	Age, maternal weight, race, breast feeding
			Age at breast development stage B3 not associated with prenatal or lactational PCB exposure categories (avg age for highest vs lowest PCB category) (p for trend = 0.41 and 0.69)	Prenatal 10.1/11.1 yr Lactational 11.6/11.9 yr	As above
			Age at genital development stage G3 in boys not associated with prenatal or lactational PCB exposure categories (avg age for highest vs lowest PCB category) (p for trend = 0.78 and 0.07)	Prenatal 12.4/13.0 yr Lactational 11.5/12.4 yr	As above
			Age at menarche not associated with prenatal or lactational DDE exposure categories (avg age for highest vs lowest DDE category) (p for trend = 0.83 and 0.95)	Prenatal 12.9/13.3 yr Lactational 12.7/12.9 yr	As above

			Age at breast development stage B3 not associated with prenatal or lactational DDE exposure categories (avg age for highest vs lowest DDE category) (p for trend = 0.65 and 0.37)	Prenatal 11.0/11.6 yr Lactational 10.1/11.5 yr	As above
			Age at genital development stage G3 in boys not associated with prenatal or lactational DDE exposure categories (avg age for highest vs lowest DDE category) (p for trend = 0.95 and 0.77)	Prenatal 12.5/12.6 yr Lactational 12.0/12.4 yr	As above
(Colon et al. 2000), Puerto Rico	Hospital-based case-control study, 41 cases premature breast development in girls, 35 control girls	Measured serum diethyl and dibutyl phthalate levels	Premature breast development associated with serum diethyl phthalate levels (avg levels in cases and controls)	70 vs 450 µg/L (p < 0.05)	
(Blanck et al. 2000), Michigan	Cohort study, 327 daughters of mothers in the Michigan PBB registry, age 5-24 yr; information from mothers and daughters at least age 18 yr on daughter's ages at pubertal changes with aid of Tanner stage drawings	Daughters were exposed prenatally to PBBs; only 14% of mothers had serum PBBs and PCBs measured at daughter's birth; other mothers were sampled later; estimated maternal serum PBB and PCB levels at daughter's birth by maternal decay rate model based on maternal postnatal serum PBB levels	Likelihood of being post-menarche associated with maternal serum PBB levels among breastfed but not non-breastfed daughters (respective hazard ratios for maternal serum PBB ≥ 7 vs ≤ 1 µg/L)	3.4 (CI 1.3-9.0) 0.8 (CI 0.3-1.8)	Maternal age at menarche, maternal PCB exposure, maternal age at daughter's birth, maternal education, prenatal smoking, household income
			Breast development among daughters age 8-18 yr (n=161) not associated with maternal serum PBB levels among breastfed or non-breastfed	1.2 (CI 0.2-6.4) 0.5 (CI 0.2-1.9)	Daughter's age, usual physical activity, maternal education, age at daughter's birth,

			daughters (respective hazard ratios for maternal serum PBB ≥ 7 vs ≤ 1 $\mu\text{g/L}$)		PCB exposure, years of farm chemical use
			Likelihood of being in pubic hair stage 2 or above among daughters age 8-18 yr (n=161) associated with maternal serum PBB levels among breastfed but not non-breastfed daughters (respective hazard ratios for maternal serum PBB ≥ 7 vs ≤ 1 $\mu\text{g/L}$)	20 (CI 2.8-138) 0.9 (CI 0.2-4.3)	Daughter's age, maternal PCB exposure, education, age at daughter's birth, 1 st trimester alcohol consumption, smoking during year before daughter's birth
			Little association between age at menarche or Tanner stage and perinatal PCB exposure (reported without supporting data in paper)		
(Strom et al. 2001), USA	Retrospective cohort study, 811 persons age 20-34 yr who were randomized at birth to receive soy (n=248) or cow milk formula (n=563); self-reported pubertal maturation, menstrual and reproductive history	Those fed soy formula were exposed to relatively high phytoestrogen levels	Avg age at menarche similar in two groups (avg age in soy and cow milk formula groups)	12.6 vs 12.7 yr	
			Avg age at first wearing bra identical in two groups	12.3 yr	
			Age at boy's voice change similar in two groups	14.3 vs 14.0 yr	
			Age at first ejaculation similar in two groups	13.2 vs 13.0 yr	
(Boisen et	Review of literature and hypothesis	Poor Leydig cell and	Environmental and genetic		

al. 2001), Denmark	for a testicular dysgenesis syndrome	Sertoli cell function, respectively, cause androgen insufficiency and impaired germ cell differentiation <i>in utero</i>	factors interact periconceptually to disrupt testicular development and cause cryptorchidism and hypospadias <i>in utero</i> and reduced semen quality and testicular cancer later		
(Staessen et al. 2001), Antwerp, Belgium	Cross-sectional study, 200 adolescents, mean age 17 yr, life-long residents of two areas with known PCDD and lead contamination from waste incineration, lead and other industries and comparison group from a non-contaminated area; physicians assessed sexual maturation stage including testicular volume	Measured PCBs, and TCDD-like compounds (calux <i>in vitro</i> assay of AhR activation)	Borderline association between less than adult genital development in boys and serum PCBs (relative risk for a doubling of serum PCBs)	3.8 (CI 0.9-8.0)	(+)
			Less than adult breast development in girls associated with serum TCDD -like activity level (relative risk for a doubling of serum dioxin activity)	2.3 (CI 1.2-4.5)	+
			Testicular volume significantly lower in contaminated regions	+	
(Den Hond et al. 2002), Belgium	Cross-sectional study, see Staessen et al. 2001 above, 200 youth age 15-19 yr	Measured serum levels of PCBs (138, 153, 180) and TCDD -like compounds (chemically activated luciferase expression (CALUX) assay)	Boys – reduced testicular volume among those in exposed regions (total testicular volumes for rural vs 2 urban regions)	47 vs 42-43 ml (p < 0.005)	Age, BMI, parental social class
			No association between testicular volume and serum levels of TCDD-like organochlorine compounds		As above

			Boys – delayed genital development associated with doubling of serum PCBs but not serum TCDD-like activity (odds ratio for doubling of serum PCBs)	3.8 (p= 0.06)	As above
			Boys – reduced pubic hair growth associated with doubling of PCBs but not serum TCDD-like activity (odds ratio for doubling of serum PCBs)	2.7 (p=0.06)	As above
			Girls – delayed breast development associated with doubling of serum TCDD-like activity but not with serum PCBs (odds ratio for doubling of serum TCDD-like activity)	2.3 (p=0.02)	Age, BMI, oral contraceptive use, parental social class
(Mol et al. 2002), Faroe Islands	Birth cohort study, 196 boys; examined by pediatrician at avg age of 14 yr for Tanner stage pubertal changes and testicular volume; morning urine sample examined for presence of sperm and measured current serum testosterone, FSH, LH, SHBG, inhibin B	Cord tissue PCB levels; tertiles were < 1.5, 1.5-3.0 and > 3.0 ng/g	Morning spermaturia not associated with cord tissue PCB levels (GM for spermaturia yes/no)	2.0 vs 1.8 ng/g (p = 0.59)	
			Testicular volume not associated with cord tissue PCB tertile (volume 3 rd vs 1 st tertiles, p for trend = 0.30)	7.5 vs 6.8 ml	
			Pubic hair Tanner stage not associated with cord tissue PCB	1.9 vs 1.9	

			tertile (stage for 3 rd vs 1 st tertiles, p for trend = 0.63)		
			External genitals Tanner stage not associated with cord tissue PCB tertile (stage for 3 rd vs 1 st tertiles, p for trend = 0.25)	2.1 vs 2.1	
(Selevan et al. 2003), NHANES III, USA	Cross-sectional study, 2,186 girls age 8-18 yr (African-American, Mexican-American, non-Hispanic white); assessed age at menarche and Tanner stage for pubic hair and breast development	GM blood lead 1.4, 1.7 and 2.1 µg/dL for non-Hispanic whites, Mexican Americans and African Americans	Delayed breast development associated with blood lead in African-American and Mexican-American girls (respective odds ratios of reaching a successive pubertal stage for girls with blood lead levels of 3 vs 1 µg/dL)	0.6 (CI 0.4-1.0) 0.8 (CI 0.6-0.9)	Age, age squared, height, BMI, family income, ever smoked 100 cigarettes, dietary iron, vitamin C and calcium
			Delayed pubic hair development associated with blood lead in African-American and Mexican-American girls (respective odds ratios of reaching a successive pubertal stage for girls with blood lead levels of 3 vs 1 µg/dL)	0.6 (CI 0.4-1.0) 0.7 (CI 0.5-0.9)	Age, age squared, height, family income, ever smoked 100 cigarettes, anemia, dietary iron and vitamin C
			Age at menarche associated with blood lead in non-Hispanic white and African-American girls (respective odds ratios for girls with blood lead levels of 3 vs 1 µg/dL)	0.7 (CI 0.6-1.0) 0.8 (CI 0.6-1.0)	Height, BMI, family income, anemia, dietary calcium

Pubertal development and related outcomes: summary

Genital development (boys and girls)

PCBs and TCDD – The North Carolina and Michigan birth cohort studies found no association between pubertal stage attainment among adolescents and prenatal or lactational PCB exposure (Gladen et al. 2000, Blanck et al. 2000). A Belgian cross-sectional study of adolescents showed that delayed genital development was associated with current serum PCBs or TCDD-like activity levels in males but not in females (Staessen et al. 2001, Den Hond et al. 2002). The Michigan birth cohort study found associations between *accelerated* menarche and pubic hair development and maternal serum PBB levels among breastfed but not among non-breastfed daughters (Blanck et al. 2000). A small birth cohort study in the Faroe Islands showed that morning spermaturia, testicular volume and Tanner stages of pubic hair and genital development among boys age 14 yr were not associated with cord tissue PCB levels (Mol et al. 2002).

DDT/DDE – The North Carolina and Michigan birth cohort studies found no association between pubertal stage attainment among adolescents and prenatal or lactational DDE exposure (Gladen et al. 2000, Blanck et al. 2000).

Lead – A cross-sectional study of over 2,000 girls NHANES III showed that delayed menarche and pubic hair development were associated with blood lead levels in the range below 10 µg/dL in at two of the three major ethnic subgroups studied (Selevan et al. 2003).

Phytoestrogens – Follow-up at age 20-34 yr of persons randomized at birth to receive soy or cow milk formula showed no associations between average age at menarche and voice change or first ejaculation in boys and exposure to soy formula, a rich source of phytoestrogens (Strom et al. 2001).

Breast development (girls)

PCBs/TCDD – A Belgian cross-sectional study showed an association between delayed breast development in girls and serum TCDD activity but not with serum PCBs (Den Hond et al. 2002). The Michigan birth cohort study showed that breast development was not associated with maternal serum PBB levels among breastfed or non-breastfed daughters (Blanck et al. 2000).

Lead – A cross-sectional study of over 2,000 girls NHANES III showed that delayed breast development was associated with blood lead levels < 10 µg/dL in at two of the three major ethnic subgroups studied (Selevan et al. 2003).

Phthalates – A small case-control study of premature breast development in Puerto Rico showed an association with serum diethyl phthalate levels (Colon et al. 2000).

Phytoestrogens – Follow-up at age 20-34 yr of women randomized at birth to receive soy or cow milk formula showed no association between average age at first wearing a bra and exposure to soy formula, a rich source of phytoestrogens (Strom et al. 2001).

Other

Follow-up of sons of women who participated in a randomized clinical trial of prenatal DES therapy showed that exposed sons were less likely to be living as married (Beral and Colwell 1981). A cross-sectional study of adolescents showed inverse associations between serum LH and FSH and blood lead levels among boys but not girls with blood lead levels ≥ 10 µg/dL (Vivoli et al. 1993).

4. Semen quality

Reference, location	Design	Exposure	Results	Association ^f	DR ^g	Covariates
(Bush et al. 1986), Albany, New York	Fertility clinic-based study, 133 men (33 fertile, 50 subfertile, 50 infertile); assessed semen quality	Analyzed semen samples for PCBs (74 congeners), p,p'-DDE, hexachlorobenzene and mirex	Fertility status not associated with semen PCB, DDE, hexachlorobenzene or mirex levels (stated without presenting data in paper)			
			Sperm motility inversely associated with semen PCB levels (% motility index decrement per µg/g increase in semen concentrations of PCB-52, 118, 138 and 153)	-32, -84, -46, -100% (p < 0.05 for each relationship)		
(Birnbaum 1995), USA	Literature review, developmental effects of dioxins in experimental animals	Relatively high doses of TCDD and dioxin-like chemicals can cause testicular and ovarian atrophy in animals	Prenatal exposure to low doses of TCDD and dioxin-like chemicals can cause reduced masculinity (reduced semen quality) and feminization (decreased anogenital distance, reduced weight of testicles and accessory sex organs) in male			

^f Entries in this column include odds ratios, relative risks and certain other statistical measures of association as published in original epidemiologic studies; an entry of '+' means the measure of association was not an odds ratio or relative risk and was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

^g 'DR' refers to a dose-response relationship in an epidemiologic study; an entry of '+' means the measure of dose-response relationship used in the citation was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

			animals and cleft phallus/clitoris, hypospadias and delayed vaginal opening in female animals
(Brouwer et al. 1995), Netherlands	Review of developmental toxicity of PHAHs in experimental animals	Prenatal and lactational exposure to PCBs, PCDDs and PCDFs can cause reduced semen quality and ejaculation, impaired sex organ and urogenital tract development and reduced fertility of offspring in experimental animals	LOAELs for these effects occur at TEQ body burden levels within the range of current background human body burdens
(Giusti et al. 1995), USA	Review of literature on long-term health effects of prenatal DES exposure ^h	Mothers prenatally exposed to DES therapy	Limited and inconsistent evidence of reduced semen quality in sons (lower sperm concentration, increased abnormal sperm morphology)
(Longnecker et al. 1997), USA	Review of human health effects of PCBs, DDT and related organochlorines	PCBs and p,p'-DDE comprise the bulk of organochlorine residues in human tissues	Inconclusive evidence for an association between semen quality and occupational or ambient PCB exposure
(Sever et al. 1997), USA	Review of epidemiologic literature on occupational pesticide exposure and reproductive/developmental effects	Sufficient evidence for associations between reduced semen quality and occupational exposure to	Limited evidence for an association between reduced semen quality and occupational exposure to

^h Although DES was a medical drug and not an environmental contaminant, it is included here to show the potential health effects of prenatal exposure to a potent hormone.

		dibromochloropropane (DBCP) and chlordecone (Kepone)	ethylene dibromide		
(Brouwer et al. 1998), The Netherlands	Review of health risks to infants of perinatal exposure to PCBs, dioxins and related compounds by a World Health Organization working group	Perinatal exposure of rodents to TCDD caused reduced anogenital distance, delayed testis descent and reduced sperm counts in male offspring and clitoral clefting in female offspring	Perinatal exposure of male rodents to TCDD caused partial demasculinization of sexual behaviour during adulthood; no effect of same exposure on sexual behaviour of female offspring during adulthood		
(Larsen et al. 1998a), Denmark	Cohort study, followed 161 farmers who used pesticides over a growing season and 87 organic farmers who avoided pesticides; assessed semen quality just before or during early spray season and about 12-18 wk after the first spraying day; measured serum LH, FSH, SHBG, inhibin B	Self-reported information on pesticide spraying including date, product name, hectares, hours, spray and protective equipment	Total sperm count change during growing season not associated with pesticide use (difference in sperm counts before and during growing season, pesticide users vs non-users)	-30x10 ⁶ vs -32x10 ⁶ (p > 0.05)	Spillage, fever, duration of abstinence, interval between sampling and analysis
			% normal sperm heads change during growing season <i>positively</i> associated with pesticide use (difference in % normal sperm heads before and during growing season, pesticide users vs non-users)	+3% vs -4.5% (p < 0.01)	As above
			Index of abnormal sperm chromatin structure change during growing season <i>inversely</i> associated with pesticide use (difference in abnormal sperm chromatin index before and during	-1.7 vs +2.5 (p < 0.01)	As above

			growing season, pesticide users vs non-users)		
(Tielemans et al. 1999a), The Netherlands	Case-control study, based on infertility clinics; assessed 692 men with sperm concentration < 20x10 ⁶ /ml or < 50% motile or < 14% normal morphology (case group A), 267 men with sperm concentration < 5x10 ⁶ /ml or < 10% motile or < 5% normal morphology (case group B) and 61 men with azoospermia (no sperm)(case group C), 207 controls with sperm concentration ≥ 20x10 ⁶ , ≥50% motile sperm and ≥14% normal morphology; assessed total case groups and subgroups with primary infertility defined as never having fathered a child	Self-reported occupational history, job-exposure matrix; urine from 69 cases and 20 controls tested for nickel, chromium, cadmium and manganese	No association between semen quality and urinary manganese (mean urinary manganese levels in cases and controls); also no associations with urinary cadmium, chromium or nickel	0.52 vs 0.56 μg/g creatinine (p = 0.68)	Female partner's age, education, clinic
			Poor semen quality (case group A) not associated with welding fume exposure (33 exposed cases)	1.1 (CI 0.5-2.3)	As above
			Poor semen quality (case group A) not associated with pesticide exposure (12 exposed cases)	1.2 (CI 0.3-4.4)	As above
			Poor semen quality (case group A) not associated with solvent exposure (82 exposed cases)	1.0 (CI 0.6-1.6)	As above
			Borderline association between poor semen	1.9 (CI 0.9-4.2)	As above

			quality (case group A) in subgroup with primary infertility and exposure to aromatic solvents (49 exposed cases)		
			Azoospermia (case group C) associated with exposure to aromatic solvents in subgroup with primary infertility	3.4 (CI 1.5-7.7)	As above
		18/99 cases and 1/18 controls had detectable levels of solvent metabolites in urine	Borderline and imprecise association between poor semen quality (case group A) and urinary solvent metabolite levels (odds ratio)	7.0 (CI 0.8-60)	As above
(Slutsky et al. 1999), 12 countries	Cohort study of 21,857 pesticide applicators working on banana and pineapple plantations; assessed semen quality	Self-reported DBCP exposure	24% had azoospermia (no sperm in semen)		
(Padungtod et al. 1999), China	Cohort study, 13 male pesticide factory workers and 16 unexposed textile factory workers, age 20-40 yr; assessed sperm aneuploidy (disomy of chromosome 18 and X and Y chromosomes) using FISH method (scored at least 2500 sperm per person)	Pesticide production workers exposed to the organophosphates ethyl parathion and methamidophos; median 8-hr avg personal air parathion level of 0.02 mg/m ³	Sperm aneuploidy associated with organophosphate pesticide production exposure (aneuploidy rates among exposed vs unexposed men were 1.1 vs 0.6 per 1,000 sperm) (rate ratio shown)	1.7 (CI 1.2-2.3)	
			Sperm concentration and motility similar in exposed and unexposed men		

(Padungtod et al. 2000), China	Cohort study, 20 male pesticide factory workers and 23 unexposed textile factory workers; assessed semen quality	See Padungtod et al. 1999 above; measured skin patch pesticide, personal air pesticide, urinary p-nitrophenol and plasma AChE levels	Sperm concentration was lower among exposed men (linear regression coefficient)	-0.6 (CI -0.9 to -0.2)	Age, abstinence period, smoking
			% motile sperm was lower among exposed men (linear regression coefficient)	-10 (CI -19 to -1.6)	As above
			Borderline lower % normal sperm morphology among exposed men (linear regression coefficient)	-5.0 (CI -11 to 0.7)	As above
(Selevan et al. 2000), Czech Republic	Cross-sectional study, 154 men living in a highly industrialized region with air pollution, 118 men from a relatively unpolluted rural region, age 18 yr; assessed semen quality, self-reported exposures, conducted sperm chromatin structure assay	Assessed semen quality in late winter (higher air pollution) and late summer; ambient air pollution monitoring data (PM ₁₀ , TSP, SO ₂ , CO, NO _x); avg PM ₁₀ levels in polluted region during 90 days before winter 1, summer and winter 2 semen collections were, respectively, 185, 36 and 61 µg/m ³ ; corresponding levels in less polluted region were 66, 18 and 29 µg/m ³	Sperm count not associated with exposure to medium or high air pollution levels during 90 days before semen collection (beta, high vs low exposure)	0.11 (CI -0.05 to 0.27)	Smoking, alcohol, caffeine, abstinence duration, fever, wears briefs, work/hobbies with metals, work/hobbies with solvents
			% normal sperm morphology inversely associated with exposure to medium or high air pollution levels during 90 days before semen collection (beta, high vs low exposure)	-0.84 (CI -1.15 to -0.53)	As above

			% sperm with abnormal chromatin increased after exposure to high air pollution levels during 90 days before semen collection (beta, high vs low exposure)	0.30 (CI 0.08-0.52)		As above
(Abell et al. 2000a), Denmark	Cohort study, 122 male greenhouse workers; assessed semen quality and measured serum testosterone, FSH, LH, cholinesterase	Self-reported occupational history incl work task diaries, data on greenhouse pesticide applications; assessed exposure based on (i) greenhouse area treated during previous 3 mos, (ii) hr/d in contact with pesticide-treated cultures and protective practices, (iii) tertiles of estimated dermal pesticide exposure	Borderline inverse association between sperm concentration and estimated dermal pesticide exposure (mean concentration among high vs low level exposure groups); p for trend = 0.1	51 vs 93 (10 ⁶ /ml)	(+)	Age, urogenital disease, fever, spillage, abstinence duration, cryptorchidism
		Non-significant lower plasma cholinesterase in highest compared to lowest pesticide exposure category	Sperm concentration inversely associated with duration of exposure (mean concentrations, ≥10 vs < 5 yr, p for trend = 0.08)	56 vs 92 (x10 ⁶ /ml)	(+)	As above
			Sperm velocity not associated with estimated dermal pesticide exposure; p for trend = 0.3			As above plus interval from sampling to testing
		* categories of % normal sperm morphology not stated in publication	Inverse association between proportion normal sperm morphology and estimated dermal pesticide	0.7 (CI 0.5-1.0)	+	As above

			exposure (? odds ratio of % normal sperm morphology > median*, high vs low exposure); p for trend = 0.02	
(Guo et al. 2000), Taiwan	Cross-sectional study, 12 men age 16-20 yr prenatally exposed to PCBs and related toxicants during the Yucheng incident, 23 unexposed men matched for age; assessed semen quality	Prenatal exposure to PCBs and PCDFs in cooking oil consumed by mothers	Semen volume and sperm concentration not associated with PCB/PCDF exposure	Groups similar with regard to age and weight
			Abnormal sperm morphology associated with PCB/PCDF exposure (% abnormal, exposed vs unexposed)	38 vs 26% (p < 0.001)
			Reduced sperm motility associated with PCB/PCDF exposure (% motile, exposed vs unexposed)	35 vs 57% (p = 0.006)
			Hamster oocyte penetration reduced among exposed group (% penetrated, exposed vs unexposed)	66 vs 74% (p = 0.02)
(Swan 2000), USA	Review of literature on long-term effects of prenatal DES exposure	Prenatal maternal exposure to DES therapy	Limited and inconsistent evidence of reduced semen quality among DES-exposed sons	
(Mitchell et	Controlled exposure study, 14 men	Consumed 1 soy extract	No significant changes in	

al. 2001), Edinburgh, Scotland	age 18-35 yr; assessed semen quality and testicular volume twice before, twice during and 3 times after consumption of dietary phytoestrogens supplements	tablet/day containing 40 mg of the phytoestrogens genestein, daidzein and glycitein for 2 mos	sperm concentration, counts, motility or morphology after consumption of phytoestrogen dietary supplements			
(Oliva et al. 2001), Argentina	Cross-sectional study, 189 male partners from couples at infertility clinics; assessed semen quality and serum FSH, LH, testosterone and estradiol-17 β levels	Self-reported occupational exposures during previous 10 yr	Borderline inverse association between sperm count and solvent exposure	2.5 (CI 0.8-7.9)		Age, abstinence duration, income, clinic, BMI, smoking
			< 30% normal sperm associated with solvent exposure	3.0 (CI 1.0-9.0)		As above
(Boisen et al. 2001), Denmark	Review of literature and hypothesis for a testicular dysgenesis syndrome	Poor Leydig cell and Sertoli cell function, respectively, cause androgen insufficiency and impaired germ cell differentiation <i>in utero</i>	Environmental and genetic factors interact periconceptually to disrupt testicular development and cause cryptorchidism and hypospadias <i>in utero</i> and reduced semen quality and testicular cancer later			
(Dallinga et al. 2002), The Netherlands	Cross-sectional study, 34 men with male-factor subfertility (progressively motile sperm counts (PMSC) $\leq 10^6$ /ml) and 31 male with PMSC $\geq 10^7$ /ml, proven <i>in vitro</i> fertility and partners of women with female-factor subfertility	Measured HCB, DDE, DDT and PCBs (118, 138, 153, 180) in blood and seminal plasma and PCB metabolites in blood	% normal sperm morphology <i>positively</i> associated with blood levels of individual and total PCB levels in total group (R ² for total PCB levels)	R ² = 0.15 (p = 0.02)	+	Smoking was not a confounder
		Blood PCB levels about 20-fold higher than seminal plasma levels; total PCBs in blood and seminal plasma	Sperm count and motility not associated with individual or combined blood or seminal plasma			As above

		significantly correlated ($R^2 = 0.38$, $p = 0.05$)	PCB levels in total group (results stated without presenting data)		
			<i>Positive</i> associations between seminal plasma total PCB levels and sperm count, PMSC and % normal sperm morphology (respective correlations)	$R^2 = 0.79$ ($p = 0.0005$)	
				$R^2 = 0.86$ ($p = 0.0001$)	
				$R^2 = 0.40$ ($p = 0.05$)	
			Sperm counts <i>inversely</i> associated with blood PCB metabolite levels within the subgroup of fertile men	$R^2 = 0.14$ ($p = 0.04$)	+ As above
			PMSC <i>inversely</i> associated with blood PCB metabolite levels within the subgroup of fertile men	$R^2 = 0.17$ ($p = 0.02$)	+ As above
			Similar average blood and seminal plasma HCB, DDE and DDT levels in apparently fertile and non-fertile men		As above
(Hauser et al. 2002), Boston	Cross-sectional study, 29 men tested at andrology laboratory; 18 had normal semen quality and served as comparison group for 11 men with abnormal semen quality	Measured serum PCBs and DDE in both groups; results for men with abnormal vs normal semen quality – PCBs (mean 242 vs 202 ng/g lipid) and DDE (mean 354 vs 240 ng/g lipid)	Reduced sperm motility associated with higher PCB levels (statistical significance not assessed)		

(Hauser et al. 2003), Boston	Cross-sectional study, 212 male partners of a sub-fertile couple including a subgroup of 98 men who had normal semen quality who served as a comparison group for men with abnormal semen quality	Measured serum total PCBs (57 congeners)(GM 226, range 56-1733 ng/g lipid), estrogenic PCBs (GM 16, range 3.9-205 ng/g lipid), dioxin-like PCBs (GM 82, range 20-519 ng/g lipid), enzyme-inducing PCBs (GM 93, range 20-830 ng/g lipid) and DDE (GM 275, range 64-8912 ng/g lipid)	Sperm concentrations below 20×10^6 /ml not associated with total, individual, estrogenic, dioxin-like or enzyme-inducing serum PCB congener levels (odds ratio for total PCBs, 3 rd vs 1 st tertiles, p for trend = 0.8)	0.9 (CI 0.3-2.4)	Age, abstinence time, smoking
			< 50% motile sperm associated with serum PCB-138 levels (odds ratio for 3 rd vs 1 st tertiles, p for trend = 0.03) but not with other PCB exposure indices	2.4 (CI 1.1-5.0)	+ As above
			< 4% normal sperm morphology associated with serum PCB-138 levels (odds ratio for 3 rd vs 1 st tertiles, p for trend = 0.04) but not with other PCB exposure indices	2.5 (CI 1.1-6.0)	+ As above
			Sperm concentrations below 20×10^6 /ml not associated with serum DDE levels (odds ratio for 3 rd vs 1 st tertiles, p for trend = 0.9)	1.0 (CI 0.4-2.5)	As above
			< 50% motile sperm not associated with serum DDE levels (odds ratio for 3 rd vs 1 st tertiles, p for	1.5 (CI 0.7-3.1)	As above

			trend = 0.3)			
			Abnormal sperm morphology not associated with serum DDE levels (odds ratio for 3 rd vs 1 st tertiles, p for trend = 0.8)	1.1 (CI 0.5-2.8)		As above
(Richthoff et al. 2003), Sweden	Cross-sectional study, 305 male military conscripts age 18-21 yr; measured testicular volume, semen quality parameters, blood hormone levels	Measured serum PCB-153 (median 65, range 23-250 ng/g lipid)	Testicular volume not associated with serum PCB-153 levels	r = 0.02 p = 0.7		Adjusted for BMI, length of abstinence and smoking as necessary
			Sperm motility inversely associated with serum PCB-153 levels (% decrease in motile sperm per serum PCB-153 increment of 10 ng/g lipid)	-1.0% (CI -2.0 to -0.13)	+	
(Duty et al. 2003a), Boston	Fertility clinic-based study, 168 male partners of subfertile couples; assessed semen quality	Measured 8 urinary phthalate monoester metabolites	Borderline dose-response relationship between sperm concentration 20×10^6/ml and urinary monobutyl phthalate levels (odds ratios, 3 rd vs 1 st tertile, p for trend = 0.07)	3.3 (CI 0.9-13)	(+)	Age, abstinence time, smoking
			Dose-response relationship between sperm concentration 20×10^6/ml and urinary monobenzyl phthalate levels (odds ratios, 3 rd vs 1 st tertile, p for trend = 0.02)	5.5 (CI 1.3-24)	+	As above
			Dose-response relationship	3.0	+	As above

			between <50% motile sperm and urinary monobutyl phthalate levels (odds ratios, 3 rd vs 1 st tertile, p for trend = 0.02)	(CI 1.2-7.6)		
			Borderline dose-response relationship between <50% motile sperm and urinary monobenzyl phthalate levels (odds ratios, 3 rd vs 1 st tertile, p for trend = 0.1)	2.1 (CI 0.8-5.3)	(+)	As above
			Borderline dose-response relationship between <4% normal sperm morphology and urinary monobutyl phthalate levels (odds ratios, 3 rd vs 1 st tertile, p for trend = 0.1)	2.2 (CI 0.8-6.1)	(+)	As above
			Borderline dose-response relationship between <4% normal sperm morphology and urinary monobenzyl phthalate levels (odds ratios, 3 rd vs 1 st tertile, p for trend = 0.1)	2.2 (CI 0.8-6.0)	(+)	As above
(Duty et al. 2003b), Boston	See Duty et al. 2003 above; assessed sperm DNA integrity using the neutral comet assay (an index of DNA strand breaks)	See Duty et al. 2003 above	Length of DNA "comet" (an index of DNA strand breaks) associated with urinary monoethyl phthalate levels (avg increase per interquartile range increase in monoethyl phthalate	3.6 μ m (CI 0.7-6.5)		Age, smoking

			level)(443 µg/L)
(National Academy of Sciences 2003), USA	Literature review, potential health effects from phenoxy herbicides contaminated with TCDD	2,4-D and 2,4,5-T were contaminated with TCDD	There is insufficient evidence to determine if phenoxy herbicide exposure is associated with reduced semen quality and infertility

Semen quality: summary

PCBs, dioxins and related compounds

A fertility clinic-based cross-sectional study showed that sperm motility (but not fertility – see next section) was inversely associated with concentrations of PCB-52, 118, 138 and 153 in semen [note: this is one of the few epidemiologic studies that measured environmental toxicants in semen] (Bush et al. 1986). A review of epidemiologic studies concluded that there was inadequate evidence for associations between semen quality and occupational or background exposure to PCBs (Longnecker et al. 1997). Studies published since this review have shown fairly consistent associations between reduced semen quality and PCB exposure indices. A small study of Yucheng men prenatally exposed to high-levels of PCBs/PCDFs showed that, compared to unexposed men, they had similar sperm counts but more frequent abnormal sperm morphology, reduced sperm motility and reduced ability of sperm to penetrate hamster oocytes *in vitro* (Guo et al. 2000). One very small study and three larger cross-sectional studies of males in couples with fertility problems all showed inverse associations between sperm motility indices and various serum PCB indices. Among the three larger studies, (i) Dallinga et al. (2002) found an *inverse* dose-response relationship between progressively motile sperm counts (among men with normal total sperm counts) and blood PCB metabolite levels but *positive* associations between blood and seminal plasma total PCB levels and one or more semen quality indicators, (ii) Hauser et al. (2003) showed dose-response relationships between reduced sperm motility and abnormal morphology and serum PCB-138 (PCB-138 is a non-TCDD-like PCB congener frequently detected in the general population) but not total, estrogenic or TCDD-like serum PCB levels, (iii) Richthoff et al. (2003) showed an inverse dose-response relationship between sperm motility and PCB-153 levels (also a non-coplanar PCB congener frequently detected in the general population), (iv) there was a *positive* dose-response relationship between abnormal sperm morphology and serum non-coplanar PCB levels (Dallinga et al. 2002), (v) total sperm counts were not associated with individual or aggregated blood or seminal fluid PCB levels but were inversely associated with blood PCB metabolite levels among the subgroup of men with normal sperm counts (Dallinga et al. 2002). Reviews of toxicology studies (Birnbaum 1995, Brouwer et al. 1995, 1998) concluded that prenatal exposure of experimental animals to relatively low doses of TCDD or TCDD-like organochlorines can cause reduced semen quality. Boisen et al. (2001) hypothesized that environmental and genetic factors interact periconceptually to disrupt testicular development, causing cryptorchidism and hypospadias in children *in utero* and reduced semen quality and testicular cancer at older ages.

Pesticides

DBCP, chlordecone – A recent review concluded that there is sufficient evidence for associations between reduced semen quality and occupational exposure to dibromochloropropane (DBCP) and chlordecone (Kepone) (Sever et al. 1997). A large cohort study of pesticide applicators working on banana and pineapple plantations and exposed to DBCP showed that 24% had azoospermia (no sperm in semen) (Slutsky et al. 1999).

Ethylene dibromide – A recent review concluded that there is limited evidence for an association between reduced semen quality and occupational exposure to ethylene dibromide (Sever et al. 1997).

TCDD-contaminated phenoxy herbicides – A review of epidemiologic studies concluded that there was inadequate evidence for associations between semen quality and occupational or background exposure to TCDD-contaminated phenoxy herbicides (National Academy of Sciences, 2003).

Other/mixed pesticide exposures – A Danish cohort study showed similar changes in total sperm count among pesticide-using and organic farmers during the growing season; the % abnormal sperm heads and an index of abnormal sperm chromatin structure actually decreased among pesticide-using relative to organic farmers (Larsen et al. 1998a). A small cohort of organophosphate production workers in China showed increased sperm chromosomal aneuploidy (Padungtod et al. 1999) and reduced sperm concentration and % motile sperm among exposed compared to unexposed men (Padungtod et al. 2000). A fertility clinic-based case-control study found no association between semen quality and occupational pesticide exposure (Tielemans et al. 1999a). A cohort study of Danish greenhouse workers showed dose-response relationships between reduced sperm concentration and abnormal sperm morphology and estimated dermal pesticide exposure (Abell et al. 2000a). A cross-sectional study showed no association between sperm count or motility and individual or combined blood HCB, DDE or DDT levels (Dallinga et al. 2002). However, a small cross-sectional study of young men in an endemic malaria region with indoor DDT use showed inverse associations between semen volume and total sperm counts and serum DDE levels (Ayotte et al. 2001). A small case-control study of fertile men with below median semen quality parameters showed associations with certain urinary pesticide or pesticide metabolite levels (alachlor, diazinon, atrazine) but not with some other urinary pesticide or pesticide metabolite levels (2,4-D, carbamates, chlorpyrifos) (Swan et al. 2003). A large case-control study based on fertility clinics in The Netherlands showed no association between low semen quality and self-reported pesticide exposure but there were only 12 exposed cases (Tielemans et al. 1999a). A cross-sectional study of men at fertility clinics in Argentina showed associations between low sperm counts and abnormal sperm morphology and self-reported occupational pesticide exposure (Oliva et al. 2001). A similar study in Boston showed no associations between sperm concentrations, motility or abnormal morphology and serum DDE levels (Hauser et al. 2002, Hauser et al. 2003).

Other toxicants

Solvents – A fertility clinic-based case-control study showed borderline associations between poor semen quality and occupational exposure to aromatic solvents and urinary solvent metabolite levels; azoospermia was associated with self-reported occupational exposure to aromatic solvents in the subgroup of men who had never fathered a child (Tielemans et al. 1999a). Another fertility clinic-based study showed borderline or significant associations between occupational solvent exposure and reduced sperm counts and abnormal sperm morphology (Oliva et al. 2001).

Phthalates – A fertility clinic-based study in Boston showed borderline or significant dose-response relationships between low sperm concentration, reduced sperm motility, abnormal sperm morphology and urinary metabolite levels of dibutyl and dibenzyl phthalates (Duty et al. 2003a); this study also showed an association between sperm DNA strand breaks and urinary metabolite levels of diethyl phthalate (2003b).

Metals – There were no associations between semen quality and self-reported occupational exposure to welding fumes or urinary manganese, cadmium, chromium or nickel levels (Tielemans et al. 1999a).

Outdoor air pollution – A small cross-sectional study showed an association between exposure to medium or high outdoor air pollution during the 90 days before semen collection and abnormal sperm morphology and chromatin structure but not with sperm concentration or count (Selevan et al. 2000).

Therapeutic hormones

Two reviews of studies on long-term health effects of DES concluded that there was limited and inconsistent evidence for an association between prenatal maternal DES therapy and reduced semen quality in exposed sons (Giusti et al. 1995, Swan 2000).

Phytoestrogens

A small (14 men) controlled exposure study showed no change in semen quality parameters after consumption of soy extract tablets (40 mg of genestein, daidzein and glycitein daily for 2 months) (Mitchell et al. 2001).

5. Fertility

Reference, location	Design	Exposure	Results	Association ⁱ	DR ^j	Covariates
(Lauwerys et al. 1985), Belgium	Cohort study, 85 workers exposed to airborne manganese salts, 103 workers exposed to metallic mercury vapour, 182 men in comparison groups, age 16-45 yr; assessed fertility of exposed men before and after exposure; expected number of children based on fertility of comparison group	Median airborne manganese level 0.97 (range 0.07-8.6 mg/m ³); average blood manganese level among exposed men was 1.3 (range 0.1-3.3 µg/dL); corresponding mean urinary manganese level was 4.4 (range 0.1-141) µg/g creatinine	Fertility lower in group exposed to airborne manganese salts (observed vs expected number of children)	39 vs 70.5 (p < 0.05)		Groups similar with regard to age, age of wives, duration of employment, smoking, alcohol, education, wife's occupation
		Average blood mercury level among exposed men was 1.5 µg/dL; corresponding urinary mercury level was 52 (range 5.1-272 µg/g)	No association between fertility and metallic mercury vapour exposure (observed vs expected number of children)	59 vs 65.8 (p > 0.05)		As above

ⁱ Entries in this column include odds ratios, relative risks and certain other statistical measures of association as published in original epidemiologic studies; an entry of '+' means the measure of association was not an odds ratio or relative risk and was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

^j 'DR' refers to a dose-response relationship in an epidemiologic study; an entry of '+' means the measure of dose-response relationship used in the citation was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

creatinine					
(Bush et al. 1986), Albany, New York	Fertility clinic-based study, 133 men (33 fertile, 50 subfertile, 50 infertile); assessed semen quality	Analyzed semen samples for PCBs (74 congeners), p,p'-DDE, hexachlorobenzene and mirex	Fertility status not associated with semen PCB, DDE, hexachlorobenzene or mirex levels (stated without presenting data in paper)		
(Wilcox et al. 1995), Chicago	Birth cohort study, 253 men exposed to DES <i>in utero</i> in a randomized clinical trial during 1950-1952, 241 unexposed men; assessed self-reported time to conception in most recent pregnancy	Maternal prenatal DES therapy during a randomized clinical trial	Fecundability ratio similar in two groups (exposed vs unexposed)	0.9 (CI 0.7-1.1)	Frequency of intercourse, alcohol and smoking of both partners, caffeine (female partner), other factors
(Giusti et al. 1995), USA	Review of literature on long-term health effects of prenatal DES exposure ^k	Mothers prenatally exposed to DES therapy	Daughters: increased risks of primary infertility, ectopic pregnancy, early fetal death and preterm birth		
(Smith et al. 1997), USA	Case-control study, 281 infertile women (male partners had normal semen quality), 216 fertile women	Self-reported occupational and other exposures	Infertility associated with occupational solvent exposure	1.7 (CI 1.1-2.7)	Date of onset of infertility or first pregnancy
(Larsen et al. 1998b), Denmark	Cross-sectional study, 450 traditional farmers using pesticides and 72 non-users, 94 organic farmers, 66 non-farmers; self-reported reproductive history	Self-reported pesticide use, acres treated, type of crops, use of protective equipment	Fecundability ratio not decreased among farmers using pesticides vs organic farmers	1.0 (CI 0.8-1.4)	Male and female smoking, female age, recent oral contraceptive use, parity

^k Although DES was a medical drug and not an environmental contaminant, it is included here to show the potential health effects of prenatal exposure to a potent hormone.

including time to pregnancy			Fecundability ratio not associated with years of pesticide use (≥ 16 vs < 5 yr)	1.3 (CI 0.8-1.9)		As above
			Fecundability ratio not associated with hectares of crop treated by father (≥ 60 /yr vs < 20 /yr)	1.3 (CI 0.9-1.9)		As above
			Borderline inverse association between fecundability ratio and use of manual pesticide spray equipment	0.8 (CI 0.6-1.1)		As above
(Tielemans et al., 1999b), The Netherlands	Cross-sectional study (letter to editor), 836 couples seeking <i>in vitro</i> fertilization treatment; assessed <i>in vitro</i> fertilization success (number of oocytes fertilized)	Self-reported exposures to pesticides, organic solvents, metal dust or fumes, welding fumes	<i>In vitro</i> fertilization rate not associated with male partner exposure to welding fumes			Female age, indication for <i>in vitro</i> fertilization, previous birth, female education
			<i>In vitro</i> fertilization rate not associated with male partner exposure to organic solvents			As above
(Courval et al. 1999), Michigan	Cohort study, 626 couples age 17-34 yr within cohort of Michigan anglers; assessed conception delay (unsuccessfully tried to conceive during a period of 12+ months)	Assessed lifetime sports-caught Great Lakes fish consumption	Borderline association between conception delay and male sports-caught fish consumption (odds ratio for high vs no lifetime consumption)	2.8 (CI 1.0-8.0)	+	Region, age, race, education, income, smoking, alcohol, partner's sports-caught fish consumption
			Conception delay not	1.0		As above

			associated with female sports-caught fish consumption (odds ratio for high vs no lifetime consumption)	(CI 0.4-2.4)	
(Thonneau et al. 1999a; Thonneau et al. 1999b), France and Denmark	Cross-sectional study, 142 French vineyard workers, 220 French unexposed rural workers, 326 Danish traditional farmers, 123 Danish organic farmers, 121 Danish greenhouse workers (all males); self-reported time to pregnancy	Self-reported male pesticide use during year before most recent child was born	Fecundability ratio not reduced among male Danish farmers exposed to pesticides	1.1 (CI 0.8-1.4)	Female age, male and female smoking, parity, recent use of oral contraceptives
			Fecundability ratio not reduced among male Danish greenhouse workers exposed to pesticides	0.8 (CI 0.7-1.2)	As above
			Fecundability ratio not reduced among male French vineyard workers exposed to pesticides	1.2 (CI 0.9-1.6)	As above
(Curtis et al. 1999), Ontario	Retrospective cohort study, 2,012 planned pregnancies among farm families; self-reported time to pregnancy	Self-reported farm pesticide use and male/female pesticide use activities for each month of trying to conceive plus 2 mos before attempting conception; assessed pesticide class and chemical family	Borderline association between time to pregnancy and women's use of dicamba (fecundability ratio)	0.5 (CI 0.2-1.1)	Woman's age, recent oral contraceptive use, both partner's smoking, other pesticide categories
			Borderline association between time to pregnancy and women's use of 2,4-D (fecundability ratio)	0.7 (CI 0.5-1.1)	As above

			Borderline association between time to pregnancy and women's use of organophosphates (fecundability ratio)	0.8 (CI 0.5-1.1)	As above
			Time to pregnancy not associated with men's use of herbicides, insecticides or fungicides (respective fecundability ratios)	1.1 (CI 1.0-1.2)	
				1.0 (CI 0.9-1.2)	
				0.9 (CI 0.7-1.1)	
(Buck et al. 1999), New York State Angler Cohort Study	Cohort study, 785 women within population-based cohort of licensed anglers and their partners/spouses, age 18-40 yr at baseline, limited to women who stated at baseline that they were considering or undecided about becoming pregnant within the next 3 yr; assessed self-reported conception delay (conception required 12+ menstrual cycles without contraception)	Assessed lifetime paternal Lake Ontario fish consumption (most contaminated fish in region) and estimated PCB exposure based on fish consumption and PCB levels in fish	Conception delay not associated with paternal fish consumption (odds ratio, >1/month vs never)	0.9 (CI 0.4-1.6)	Maternal age, smoking, education, income, age at menarche, ever pregnant, pregnancy loss, menstrual irregularity
			Conception delay not associated with estimated paternal PCB ingestion from fish consumption (odds ratio, >7 vs 0 mg)	0.5 (CI 0.2-1.2)	
(Buck et al. 2000), New York State Angler Cohort	Cohort study, 606 women age 21-40 yr who indicated at baseline that they were planning to or were undecided about conceiving during	Assessed Lake Ontario fish consumption and PCB ingestion	Likelihood of conceiving inversely associated with female fish consumption frequency during baseline	0.7 (CI 0.5-1.0)	Maternal smoking, gynecologic diseases, parental ages, gravidity,

Study	the next 3 yr; assessed number of at risk menstrual cycles required to become pregnant		year (> vs 0 fish meals/month)		history of fertility drugs, partner's Lake Ontario fish consumption
			Likelihood of conceiving not associated with male fish consumption frequency during baseline year (> vs 0 fish meals/month)	1.1 (CI 0.8-1.4)	As above
			Likelihood of conception not associated with estimated PCB ingestion by males or females		As above
(Yu et al. 2000), Taiwan	Cohort study, 356 women age 30-59 years exposed to PCBs 14-15 years previously during Yucheng incident, comparison group of 312 unexposed neighbourhood women; assessed reproductive experience	Serum PCB levels were measured during 1979-1981 among 258 of the exposed women; 20.6% had PCB levels of at least 100 µg/g serum	Prevalence of fertility problem not increased among exposed compared to unexposed women	1.5 vs 2.0%	Comparison group matched for age, sex and neighbourhood
			No association between fertility problem and baseline serum PCB levels among exposed women (serum PCB > 46 vs ≤ 46 µg/g)	0.9 vs 1.6%	
(Sallmen et al. 2000), Finland	Cohort study, 769 wives of men occupationally exposed to lead and other metals; assessed time to pregnancy	Detailed work history	Infertility associated with male partner occupational lead exposure (odds ratio of infertility, blood lead ≥ 52 vs < 10 µg/dL)	1.9 (CI 1.3-2.6)	Age of wife, recent contraceptive use, unplanned pregnancy, caffeine intake, year of study pregnancy termination

			Likelihood of conception not associated with male partner blood lead level in among couples with at least one previous pregnancy (odds ratio of conception, blood lead ≥ 52 vs < 10 $\mu\text{g/dL}$)	0.8 (CI 0.3-1.6)	As above
(Abell et al. 2000b), Denmark	Cohort study, 253 most recent pregnancies among 492 female greenhouse workers; assessed self-reported time to pregnancy	Self-reported occupational pesticide exposure during period when attempting conception	Likelihood of becoming pregnant inversely associated with duration of contact with plant cultures (fecundability ratio, ≥ 20 vs < 20 hr/wk)	0.7 (CI 0.5-1.0)	Maternal smoking, age, parity, education, caffeine intake, oral contraception, paternal smoking
			Likelihood of becoming pregnant inversely associated with not using gloves when handling plant cultures	0.7 (CI 0.5-1.0)	As above
			Likelihood of becoming pregnant inversely associated with high exposure (contact with cultures ≥ 20 hr/wk and did not use gloves and sprayed pesticides)	0.6 (CI 0.5-0.9)	As above
(Swan 2000), USA	Review of literature on long-term effects of prenatal DES exposure	Prenatal maternal exposure to DES therapy	DES-exposed daughters had increased risk of menstrual irregularity, infertility, ectopic pregnancy, early fetal death and preterm delivery		

			Limited and inconsistent evidence of increased risk of infertility among DES-exposed sons	
(Buck et al. 2002), New York State Angler Cohort Study	Cohort study, 102 women age 18-34 yr who intended to become pregnant (a subgroup of the New York State Angler Cohort Study); used home pregnancy test kits, defined female fecundity as number of at risk menstrual cycles required for pregnancy indicated by 2 positive home pregnancy tests (TTP)	Measured serum PCBs, DDE, HCB, mirex, aldrin, BHC, t-nonachlor and oxychlorane and blood lead, arsenic, cadmium, selenium, nickel, magnesium	PCB-206 associated with reduced likelihood of pregnancy during first at risk menstrual cycle	+
			PCB-19 associated with <i>increased</i> likelihood of pregnancy during first at risk menstrual cycle	+(but note direct of association)
			PCB-205 associated with reduced likelihood of pregnancy during first 2 or 3 at risk menstrual cycles	+
			PCB-48 and 169 associated with <i>increased</i> likelihood of pregnancy during first 2 but not during first 3 at risk menstrual cycles	+/-
			Fish consumption not associated with time to pregnancy	

(Modigh et al. 2002), Sweden	Cross-sectional study, 144 men with low or high occupational exposure in 3 plants producing or using di(2-ethylhexyl)phthalate (DEHP), 182 unexposed men; self-reported time to pregnancy	Self-reported work history, spot DEHP air measurements	Fecundability ratio not associated with DEHP exposure level during current or 1-3 previous mos (fecundability ratios for nil, low and high exposure groups for exposure during previous 3 mos)	1.0, 1.1, 1.0	Paternal age, mother's age, length of recall
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Fertility: summary

Male fertility

PCBs, dioxins, other polyhalogenated aromatic hydrocarbons – A fertility clinic-based study reported that male fertility status was not associated with semen PCB levels (stated without presenting data in paper) (Bush et al. 1986). Two Michigan cohort study of families that consume Great Lakes fish (contaminated with PCBs and other organochlorine compounds) showed that conception delay was associated with male but not with female partner sports-caught fish consumption (Courval et al. 1999). In contrast, the New York Angler Cohort Study found associations between conception delay and female but not male partner sports-caught fish consumption (Buck et al. 1999, 2000); conception delay was not associated with estimated PCB intake by male or female partners (Buck et al. 2000, 2002).

Pesticides – A fertility clinic-based study reported that male fertility status was not associated with semen DDE, hexachlorobenzene or mirex levels (stated without presenting data in paper) (Bush et al. 1986). A cross-sectional study of male Danish and French agricultural workers showed no associations between self-reported time to pregnancy and exposure to farm, greenhouse or vineyard pesticides (Thonneau et al. 1999a, 1999b). A retrospective cohort study of Ontario farm families showed no association between self-reported time to pregnancy and male partner's pesticide use (Curtis et al. 1999).

Other toxicants – A cohort study in Belgium showed that reduced male fertility was associated with occupational exposure to airborne manganese salts but not with metallic mercury vapour exposure (Lauwerys et al. 1985). A Finnish cohort study found an association between fertility and male partner blood lead level; among the subgroup of couples with at least one previous pregnancy, the likelihood of conception was not associated with male partner blood lead level (Sallmen et al. 2000). A cross-sectional study of couples seeking *in vitro* fertilization showed that *in vitro* fertilization success was not associated with male partner occupational exposure to welding fumes or organic solvents (Tielemans et al. 1999b). A cross-sectional study of men working in plants producing or using di(2-ethylhexyl)phthalate showed no associations between time to pregnancy and exposure level during the previous 3 months (Modigh et al. 2002).

DES – Follow-up of men whose mothers participated in a randomized clinical trial of prenatal DES therapy showed similar fertility among exposed and unexposed men (Wilcox et al. 1995). The latter review concluded that there was limited and inconsistent evidence of reduced fertility among exposed sons (Swan 2000).

Female fertility

PCBs – Two Michigan cohort study of families that consume Great Lakes fish (contaminated with PCBs and other organochlorine compounds) showed that conception delay was associated with male but not with female partner sports-caught fish consumption (Courval et al. 1999). In contrast, the New York Angler Cohort Study found associations between conception delay and female but not male partner sports-caught fish consumption (Buck et al. 1999, 2000). This study found that conception delay was not associated with estimated PCB intake by male or female partners (Buck et al. 2000, 2002). A recent report of this study (based on women trying to conceive and closely monitored with the aid of home pregnancy test kits) showed that PCBs-205 and 206 were associated with conception delay while PCBs-19, 48 and 169 were associated with increased likelihood of conception (Buck et al. 2002). Unlike the earlier report of this study, the recent report showed no association between conception delay and female partner sports-caught fish consumption. Follow-up of women poisoned at age 15-44yr by PCBs during the Yucheng incident and a comparison group showed similar fertility rates in the two groups and no association between fertility problems and baseline serum PCB levels (Yu et al. 2000).

Pesticides – A retrospective cohort study of Ontario farm families showed borderline associations between self-reported time to pregnancy and female partner's pesticide use including dicamba, 2,4-D and organophosphates (Curtis et al. 1999). A cohort study of couples Danish female greenhouse workers showed associations between delayed conception and self-reported occupational handling of plant cultures, handling of plant cultures without gloves and pesticide spraying (Abell et al. 2000b).

Solvents – A case-control study showed that female infertility was associated with self-reported occupational solvent exposure (Smith et al. 1997).).

DES – Two reviews of literature on long-term health effects of prenatal DES exposure concluded that exposed daughters had increased risks of menstrual irregularity, primary infertility, ectopic pregnancy, early fetal death and preterm birth (Giusti et al. 1995, Swan 2000).

6. Testicular cancer

Reference, location	Design	Exposure	Results	Association ¹	DR ^m	Covariates
(Schottenfeld et al. 1980), New York City	Hospital-based case-control study, 190 cases testicular cancer, 171 cancer controls (Hodgkin's disease, non-Hodgkin's lymphoma), 150 neighbourhood controls	Self-reported exposure information from subjects (or their mothers if age < 18 yr)	Testicular cancer associated with cryptorchidism (odds ratio, cases vs neighbourhood controls)	2.5 (CI 1.0-5.7)		
		Among 19 cases with unilateral cryptorchidism, cancer occurred on the same side in 15 cases (p < 0.01)	Borderline association between testicular cancer and prenatal maternal drug use for bleeding, spotting or threatened miscarriage (odds ratio, cases vs neighbourhood controls)	2.0 (CI 0.8-4.3)		
(Depue et al. 1983), Los Angeles	Case-control study, 98 cases testicular cancer, 107 neighbourhood controls, age 16-30 yr	Self- and mother-reported exposure information	Testicular cancer associated with cryptorchidism (9 exposed cases)	9.0 (CI 1.5-55)		Matched for age, race (white), neighbourhood, mother alive
		9 case mothers exposed to hormones: DES (2), estrogen (1), progestin (1) or pregnancy test (5)	Testicular cancer associated with 1 st trimester maternal exogenous hormone use	8.0 (CI 1.3-49)		
(Moss et al. 1986),	Case-control study, 273 cases, 273 controls matched for race	Self- and mother-reported exposure information	Testicular cancer associated with	8.3 (CI 2.8-33)		

¹ Entries in this column include odds ratios, relative risks and certain other statistical measures of association as published in original epidemiologic studies; an entry of '+' means the measure of association was not an odds ratio or relative risk and was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

^m 'DR' refers to a dose-response relationship in an epidemiologic study; an entry of '+' means the measure of dose-response relationship used in the citation was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

California	and age, age 18-39 yr		cryptorchidism (29 exposed cases)			
			Testicular cancer associated with early onset of puberty (odds ratio for age < 14 vs ≥ 14 yr) (206 exposed cases)	2.0 (CI 1.3-3.1)		
			Testicular cancer not associated with prenatal maternal hormone therapy (9 exposed case mothers)	0.9 (CI 0.3-2.6)		
(Brown et al. 1987), Washington, DC	Hospital-based case-control study, 271 cases testicular cancer, 259 cancer controls (cancers other than genital tract), age 18-42 yr	Self- and mother-reported exposure information	Testicular cancer associated with cryptorchidism (25 exposed cases)	3.7 (CI 1.5-9.5)		
(Wiklund et al. 1989), Sweden	Cohort study, 20,245 licensed agricultural pesticide applicators (99% males); mean follow-up time 12 yr (to end of 1982); 18 cases of testicular cancer during follow-up; estimated expected number from national incidence rates	20% of cohort first exposed in the 1950s; most occupations were in agriculture or forestry or both and in horticulture; commonly used pesticides were MCPA, 2,4-D, 2,4,5-T, ioxynil, dichlorprop, DDT, fenitrothion, maneb and triadimefon	Borderline increased risk of testicular cancer (SIR)	1.6 (CI 0.9-2.5)		
			Testicular cancer risk increased with time since first licensed (SIR for licensed for 10+ yr)	2.5 (CI 1.1-5.0)		
(Van den Eeden et al. 1991),	Case-control study, 323 germ cell testicular tumour cases,	Self-reported occupational histories	Non-significant increased risk of germ cell testicular	1.9 (CI 0.6-5.4)		Matched for age, race, geographic area

Washington State, USA	658 matched community controls, age 20-69 yr		cancer among farm managers (7 exposed cases)			
			Germ cell testicular cancer not associated with occupation as farm workers (12 exposed cases)	0.6 (0.3-1.3)		
(Bullman et al. 1994), Vietnam veterans, USA	Case-control study nested within cohort of U.S. Vietnam veterans, 97 testicular cancer cases, 311 controls, median age 38 yr for both groups	Exposure to Agent Orange (50:50 mixture of 2,4-D and 2,4,5-T) inferred from service record information on branch of service, type of duty and area relative to sprayed tracts	Testicular cancer not associated with proximity to sprayed tracts (odds ratio for being within 2 km of sprayed regions within 3 days of spraying vs not) (7 exposed cases)	1.4 (CI 0.5-3.8)		No confounders identified (including race, age)
(Gallagher et al. 1995), Canada (Alberta, British Columbia)	Case-control study, 510 cases testicular cancer, 996 population controls, age 15-79 yr	Self-reported exposure information	Testicular cancer associated with cryptorchidism (52 exposed cases)	3.6 (CI 2.3-5.6)		Age, ethnicity
			Borderline inverse association between testicular cancer and age at puberty (odds ratio, began shaving at age ≥ 18 vs ≤ 13 yr) (177 exposed cases)	0.6 (CI 0.3-1.2)		
(Shu et al. 1995), Children's Cancer Group, Canada and United States	Case-control study, 105 cases germ-cell tumours (36 ovarian, 24 testicular, 45 non-gonadal), 639 community controls, age < 15 yr		Germ-cell tumours associated with maternal ever-exposure to plastic or resin fumes (only 3 exposed case mothers)	12 (CI 1.9-75)		Age, sex, gestation length, maternal parity, education, prenatal smoking

			Germ-cell tumours associated with paternal ever-exposure to plastic or resin fumes (8 exposed case fathers)	2.5 (CI 1.0-6.5)		As above
(Giusti et al. 1995), USA	Review of literature on long-term health effects of prenatal DES exposure ⁿ	Mothers prenatally exposed to DES therapy	Sons: limited and inconsistent evidence for increased risk of testicular cancer			
(Knight et al. 1996), Ontario	Population-based case-control study, 495 testicular cancer cases, 974 controls, age 16-59 yr	Self-reported occupational history; coded jobs and industries	Seminoma testicular cancer inversely associated with occupational pesticide exposure (number of exposed cases not stated)	0.6 (CI 0.4-1.0)		Education
(Kristensen et al. 1996b), Norway	Cohort study, linked birth registry and 5 agricultural and horticultural censuses; 166,291 male offspring of farmers and 2.9 million person-years of follow-up; 97 testicular cancer cases (age < 40 yr); compared testicular cancer incidence rates in cohort and general rural population of Norway	Expenditures on pesticides, fertilizer, possession of tractor pesticide spraying equipment (based on agricultural census closest to time of birth)	Testicular cancer risk in sons of farmers higher than general rural population; risk higher for cases age 15-19 yr compared to total cases (odds ratios, sons of farmers vs general rural population)	age < 40 1.2 (CI 1.0-1.5) age 15-19 1.4 (CI 1.0-2.0)		
(Kristensen et al. 1996a), Norway	See Kristensen 1996b above		Testicular cancer not associated with agricultural pesticide purchases (p for trend =	0.9 (CI 0.6-1.3)		

ⁿ Although DES was a medical drug and not an environmental contaminant, it is included here to show the potential health effects of prenatal exposure to a potent hormone.

			0.49) (36 exposed case families)			
			Testicular cancer not associated with parental occupation in horticulture (10 exposed case families)	0.8 (CI 0.4-1.5)		
(Prener et al. 1996), Denmark	Population-based case-control study nested within cohort of males born during 1941-1957, 183 cases testicular cancer, 366 controls matched for DOB (median age 30 yr)	School health records of annual physician examinations	Testicular cancer associated with cryptorchidism (16 exposed cases)	5.2 (CI 2.1-13)		Birth order, birth weight, social class, YOB
			Among 11 testicular cancer cases with unilateral maldescent, the cancer occurred on the same side in 6 cases and the opposite side in 5 cases			
(Davies et al. 1996), UK	Case-control study, 129 cases testicular cancer, age 15-65 yr, 211 cancer controls, 184 population controls	Self- and mother-reported exposure information	Testicular cancer associated with cryptorchidism	7.2 (CI 2.4-22)		Age, social class, height, weight, milk consumption at age 17 yr, cryptorchidism
(Moller and Skakkebaek 1996), Denmark	Population-based case-control study, 296 cases testicular cancer, age 16-72 yr, 287 controls	Mother-reported information on prenatal exposures	Inverse association between testicular cancer and age at puberty relative to classmates (odds ratio, late vs average, p for trend = 0.06) (62 exposed cases)	0.6 (CI 0.4-0.8)	(+)	
(Hardell et al. 1997), Sweden	Population-based case-control study, 148 cases testicular	Self-reported occupational histories	Testicular cancer associated with	6. (CI 1.4-32)		

	cancer, age 30-75 yr, 315 controls		occupational polyvinyl chloride exposure but only 7 exposed cases			
(Moller 1997), Denmark	Population-based case-control study, 296 testicular cancer cases, 287 controls	Self-reported information from cases and their mothers on residential and occupational history	Testicular cancer not associated with having a mother employed in agriculture	1.2 (CI 0.6-2.7)		YOB
			Testicular cancer not associated with employment in agriculture with or without animals (respective odds ratios)	0.6 (CI 0.4-1.0) 0.7 (CI 0.3-2.1)		YOB
(Weir et al. 1998), Ontario	Population-based case-control study, 502 cases testicular cancer, age 16-59 yr, 346 case mothers, 975 controls, 522 control mothers	Self- and mother-reported information on age at pubertal events relative to peers	Testicular cancer inversely associated with late puberty (odds ratio for late onset of 3-4 puberty events vs same as peers using self- or mother-reported ratings)	0.5 (CI 0.3-0.7) 0.7 (CI 0.4-4.1)		
(Mills 1998), California	Ecologic study, assessed population-based cancer incidence rates and pesticide use by county (58 counties);	State-wide data on pounds of active ingredient applied annually in each county; farm workers in California have included many Hispanic and black males	There was a non-significant correlation between Hispanic testicular cancer incidence rates by county and atrazine use (Pearson r)	r = 0.41 (p > 0.05)		
			<i>Inverse</i> correlations between Hispanic testicular cancer incidence rates by county and captan and diazinon use (respective Pearson r's)	r = -0.43 (p < 0.05) r = -0.41 (p < 0.05)		

(Cocco and Benichou 1998), USA	Ecologic study, assessed population-based testicular cancer mortality rates in 22 US states during 1971-1994	Estimated DDT exposure by state from p,p' -DDE levels in population-based subcutaneous fat samples and tree bark	Testicular cancer mortality rates not associated with indicator of DDT use by state (regression coefficient and SE for 1991-1994 mortality rates)	0.014 (SE 0.01)		
(Hardell et al. 1998), Sweden	Population-based case-control study, 148 cases testicular cancer (101 seminoma and 47 embryonal cell tumours ^o), age 30-75 yr, 314 controls	Self-reported occupational exposure information	Testicular cancer associated with occupational plastics work	3.3 (CI 1.4-7.7)		Exposure to video display units, insect repellents, occupational plastics work
			Testicular cancer associated with insect repellent use (odds ratio for ≥ 115 vs 0 days) (24 exposed cases)	2.1 (CI 1.1-4.2)	+	As above
			Subgroup of embryonal cell testicular cancers associated with occupation in farming (11 exposed cases)	3.1 (CI 1.0-9.1)		
(Ekbom and Akre 1998), Baltic Sea countries	Descriptive epidemiology of testicular cancer, data from 9 population-based cancer registries in countries bordering on the Baltic Sea; assessed birth cohort incidence rates for 6 countries with sufficient duration of cancer		Increasing testicular cancer risk among sequential birth cohorts (more important than year of diagnosis)			

^o Embryonal cell tumours originate in testicular germ cells, i.e., cells that give rise to sperm; other germ cell testicular tumours include teratomas, choriocarcinomas and yolk sac carcinoma.

	registration (Poland, former East Germany, Norway, Finland, Denmark, Sweden)					
			Increased testicular cancer may be caused by prenatal or early-life exposures			
(Sigurdson et al. 1999), Texas	Hospital-based case-control study, 160 cases testicular cancer, age 18-50 yr, 136 friends as controls		Non-significant association between seminomas and dietary total fat (odds ratios for highest vs. lowest quartiles, p for trend = 0.08); similar association for saturated fat	1.9 (CI 0.6-5.5)	(+)	Age, education, income, cryptorchidism, total daily caloric intake
			Non-seminomas associated with dietary total fat (odds ratios for highest vs. lowest quartiles, p for trend = 0.002); similar association for saturated fat	6.3 (CI 1.9-21)	+	As above plus ethnicity
(Coupland et al. 1999), UK	Population-based case-control study, 794 testicular cancer cases, 794 controls matched by YOB, age 15-49 yr		Testicular cancer associated with cryptorchidism (odds ratios for seminomas and non-seminomas)	5.3 (CI 2.9-9.7) 3.0 (CI 1.6-5.6)		
			Testicular cancer inversely associated with age at pubertal changes (odds ratios for age at voice change ≥ 16 vs < 13 yr, seminomas and non-seminomas)	0.6 (CI 0.3-1.1) 0.3 (CI 0.2-0.7)		

(Fleming et al. 1999), USA	Retrospective cohort study, 33,658 licensed pesticide applicators in Florida (90% males), 23 cases of testicular cancer among male applicators	Exposure inferred from occupation	Testicular cancer risk higher among pesticide applicators than general population (SIR)	2.5 (CI 1.6-3.7)		Age, calendar year
			Association strongest among men licensed during earliest time period (SIR, 1975-79 vs 1990-94)	3.2 (CI 1.6-5.7)		As above
(Ohlson and Hardell 2000), Sweden	Case-control study, 148 testicular cancer cases, 314 controls, age 30-75 yr	Self-reported information on lifetime working histories and specific exposures	Testicular cancer associated with occupation as plastics worker	3.3 (CI 1.4-7.7)		
			Testicular cancer associated with use of insect repellents (odds ratio, ≥ 115 d vs 0 d)	2.1 (CI 1.1-3.7)		
(Weir et al. 2000), Ontario	Population-based case-control study, cases age 16-59 years, 346 case mothers, 522 control mothers	Mother-reported prenatal exposures	Testicular cancer associated with prenatal maternal exogenous hormone use	4.9 (CI 1.7-14)		Age, bleeding/threatened miscarriage, prenatal smoking, gestation length, cryptorchidism
			Testicular cancer associated with history of cryptorchidism	8.0 (CI 3.2-20)		As above plus exogenous hormone use
(Jacobsen et al. 2000), Denmark	Cohort study, 29,767 who had semen analysis at fertility clinic during 1963-1995; identified cancer cases by linkage to national cancer	Measured sperm concentration, motility, morphology	Testicular cancer associated with decreased semen quality at baseline (SIRs for 1, 2 or 3 subfertility indices vs	1.9 (CI 1.2-2.8) 2.7 (CI 1.1-5.5) 9.3	+	

	registry, 89 cases testicular cancer (age range not given)		none) (24, 7 and 2 exposed cases)	(CI 1.0-33)		
(Swan 2000), USA	Review of literature on long-term effects of prenatal DES exposure	Prenatal maternal exposure to DES therapy	Limited and inconsistent evidence for an association between testicular cancer and prenatal maternal DES therapy			
(Strohsnitter et al. 2001), Rochester MN, Chicago, Boston, Portland ME, Hanover NH	Cohort study, combined experience of 4 cohorts of men with known prenatal DES exposure status, 1,365 exposed men, 1,394 unexposed men; self-reported health history in 1994, reported cancer verified by medical record search and pathology review; 7 testicular cancer cases among exposed men and 2 among unexposed men; expected cases based on Connecticut Tumor Registry testicular cancer incidence rates specific for calendar year and age	Mothers of exposed men received prenatal DES therapy	Borderline increased testicular cancer risk among DES-exposed but not among unexposed men (SIRs for exposed and unexposed men)	2.0 (CI 0.8-4.2) 0.8 (CI 0.1-2.7)		
(Hardell et al. 2003), Sweden	Case-control study, 61 cases of testicular cancer, 58 population-based controls; assessed exposures of subjects and their mothers	Measured plasma DDE, hexachlorobenzene, chlordane (6 congeners), PCBs (38 congeners) among subjects and their mothers; median DDE levels among controls and their mothers, respectively, were 98 ng/g lipid (range 29-601) and 324 ng/g lipid (range 51-1,431)	Borderline association between testicular cancer (all types) and subjects' plasma hexachlorobenzene and DDE levels (respective odds ratios)	1.7 (CI 0.8-3.6) 1.7 (CI 0.8-3.7)		Age, BMI; further adjustment for breastfeeding (yes/no, duration) or smoking made little difference in risk estimates

			Testicular cancer associated with subjects' mothers' plasma hexachlorobenzene levels (odds ratio shown) but not DDE levels	4.4 (CI 1.7-12)		As above
			Association between maternal plasma hexachlorobenzene level stronger for non-seminoma compared to seminoma testicular cancer (respective odds ratios)	9.0 (CI 2.4-33) 2.1 (CI 0.6-8.2)		
(Fleming et al. 2003), USA	Retrospective cohort study, 9,471 men (98% were farmers, 2% were pesticide applicators), comparison group of 438,228 other workers; based on 1986-1994 National Health Interview Survey participants and passive follow-up by linking to national death database	Exposure inferred from self-reported occupation	Testicular cancer death rate not increased among farmers and pesticide applicators (data not shown in report)			
(National Academy of Sciences 2003), USA	Literature review, potential health effects from phenoxy herbicides contaminated with TCDD	2,4-D and 2,4,5-T were contaminated with TCDD	There is insufficient evidence to determine if phenoxy herbicide exposure is associated with testicular cancer			

Testicular cancer: summary

Pesticides

Mixed exposures – Cohort studies of licensed pesticide applicators in Sweden and Florida showed increased risks of testicular cancer in (Wiklund et al. 1989, Fleming et al. 1999). A population-based case-control study in Ontario found no association with self-reported occupations potentially exposed to pesticides

(Knight et al. 1996). Two case-control studies and a US cohort study (98% were farmers) showed that testicular cancer was not associated with occupation as farmers (Van den Eeden et al. 1991, Moller 1997, Fleming et al. 2003). The latter study had limited ability to assess the risk of testicular cancer stated this finding without providing data. Testicular cancer was not associated with maternal employment in agriculture (Moller 1997). A Norwegian farm cohort study showed an increased risk of testicular cancer compared to the general population with a higher risk among those age 15-19 years compared to older men but there was no association with agricultural pesticide purchases (Kristensen et al. 1996a). A Swedish case-control study showed associations between testicular cancer and insect repellent use and occupations in farming (Hardell et al. 1998, Ohlson and Hardell 2000).

TCDD-contaminated phenoxy herbicides – A case-control study of US veterans showed no association between testicular cancer and exposure to Agent Orange (a 50:50 mix of the phenoxy herbicides 2,4-D and 2,4,5-T) (Bullman et al. 1994). A recent review concluded that there is insufficient evidence for an association between testicular cancer and phenoxy herbicide exposure (National Academy of Sciences 2003).

DDT/DDE – An ecologic study of US state-level testicular cancer mortality rates showed no association with estimated state-level DDT use (Cocco and Benichou 1998); note that testicular cancer survival rates are quite high and mortality rates reflect both the combined risks of developing disease and experiencing treatment failure. A recent small case-control study showed that testicular cancer was marginally associated with the subjects' plasma DDE levels (Hardell et al. 2003).

Other specific pesticides – An ecologic study in California showed that testicular cancer incidence among Hispanic males was marginally associated with county-level atrazine use but was inversely associated with use of captan or diazinon (Mills 1998). A recent small case-control study showed that testicular cancer was marginally associated with the subjects' plasma hexachlorobenzene and more strongly associated with their mothers' plasma hexachlorobenzene levels; the latter relationship was especially strong among the subset of non-seminoma testicular cancers (Hardell et al. 2003).

Other toxicants

A Swedish case-control study showed an association between testicular cancer and occupation as plastics workers (Hardell et al. 1997, Hardell et al. 1998, Ohlson and Hardell 2000). A case-control study of germ cell tumours (about 60% in ovaries or testicles and 40% at other sites) showed associations with maternal and paternal occupational exposure to plastic or resin fumes (Shu et al. 1995). A hospital-based case control study showed an association between non-seminoma testicular cancer and dietary fat (Sigurdson et al. 1999); although speculative, dietary fat may be acting as a proxy for intake of fat-soluble toxicants such as PCBs and dioxins.

Prenatal maternal hormone therapy

Testicular cancer was associated with maternal 1st trimester exogenous hormone therapy (DES, estrogen, progestin or hormonal pregnancy test) in a relatively small case-control study (Depue et al. 1983) but a larger study found no relationship (Moss et al. 1986). Two literature reviews concluded that there was limited and inconsistent evidence for an association between testicular cancer and maternal prenatal DES therapy (Giusti et al. 1995, Swan 2000). Since these reviews, a large population-based case-control study in Ontario (Weir et al. 2000) showed a moderately strong association between testicular cancer and prenatal maternal exogenous hormone therapy and a cohort study in the USA (Strohsnitter et al. 2001) found a borderline association with prenatal maternal DES therapy but was limited by low statistical power.

Age at puberty

Five case-control studies have shown associations between early onset of puberty and testicular cancer (Moss et al. 1986, Gallagher et al. 1995, Moller and Skakkebaek 1996, Weir et al. 1998, Coupland et al. 1999).

Cryptorchidism

Several case-control studies have shown convincing evidence of an association between testicular cancer and cryptorchidism (Schottenfeld et al. 1980, Depue et al. 1983, Moss et al. 1986, Brown et al. 1987, Gallagher et al. 1995, Prener et al. 1996), Davies et al. 1996, Coupland et al. 1999, Weir et al. 2000). There is conflicting evidence as to whether or not the risk of testicular cancer in unilateral cryptorchidism is elevated in both the normal and the undescended testicle, cancer (Schottenfeld et al. 1980, Prener et al. 1996).

7. Other reproductive tract cancers

Reference, location	Design	Exposure	Results	Association ^p	DR ^q	Covariates
(Giusti et al. 1995), USA	Review of literature on long-term health effects of prenatal DES exposure ^r	Mothers prenatally exposed to DES therapy	Daughters: risk of cervicovaginal clear-cell adenocarcinoma from birth to age 34 yr is about 10^{-4} to 10^{-3} and is greatest for daughters exposed during gestation wk 6; risk declined with later exposures			
(Mittendorf 1995), Chicago	Review of literature on carcinogenic and teratogenic effects of prenatal DES exposure	Mothers prenatally exposed to DES therapy	367 clear cell adenocarcinomas of the vagina and cervix identified in the USA up to early 1995 among DES-exposed daughters			
			Vaginal and cervical cancers were associated with maternal DES therapy during 1 st trimester			
(Swan 2000), USA	Review of literature on long-term effects of prenatal DES exposure	Prenatal maternal exposure to DES therapy	715 clear cell adenocarcinomas of cervix and vagina identified among DES-exposed daughters by June 1999			

Other reproductive tract cancers: summary

Two reviews concluded that DES therapy of pregnant women caused cervicovaginal clear-cell adenocarcinomas of the vagina and cervix among prenatally exposed daughters with the risk being greatest for those exposed during the 1st trimester (Giusti et al. 1995, Mittendorf 1995).

^p Entries in this column include odds ratios, relative risks and certain other statistical measures of association as published in original epidemiologic studies; an entry of '+' means the measure of association was not an odds ratio or relative risk and was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

^q 'DR' refers to a dose-response relationship in an epidemiologic study; an entry of '+' means the measure of dose-response relationship used in the citation was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

^r Although DES was a medical drug and not an environmental contaminant, it is included here to show the potential health effects of prenatal exposure to a potent hormone.

8. Thyroid function

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
(Koopman-Esseboom et al. 1994), The Netherlands	Birth cohort study; 78 mother-infant pairs; assessed thyroid function; measured TT ₄ , TT ₃ , FT ₄ and TSH in maternal plasma and in infant plasma at birth and ages 2 wk and 3 mos (all except one maternal TSH value were within normal limits)	Used 24-hr breast milk samples to measure levels of 17 PCDD/PCDF (mean dioxin TEQ was 32, range 12-76, pg/g fat), 3 coplanar PCBs (77, 126, 169) and 23 non-coplanar PCBs (mean PCB dioxin-TEQ was 75, range 31-154, pg/g fat)	Pre- and postnatal maternal plasma TT ₃ and TT ₄ levels inversely associated with breast milk dioxin TEQ, coplanar-PCB TEQ and non-coplanar-PCB TEQ	r = -0.33 to -0.47 (p < 0.01)	+	None
			Maternal plasma FT ₄ and TSH levels not associated with dioxin or PCB dioxin-TEQ			None
			Neonatal cord plasma TSH levels not associated with breast milk dioxin TEQ, coplanar-PCB TEQ and non-coplanar-PCB TEQ			None
			Infant plasma TSH levels at ages 2 wk and 3 mos associated with breast milk dioxin TEQ, coplanar -PCB TEQ and non-coplanar-PCB TEQ	r = 0.31-0.41 (p < 0.01)	+	None

			Among breastfed infants, plasma TSH levels at 2 wk associated with high breast milk dioxin TEQ (TSH increment for > 31 vs < 31 pg/g fat)	0.7 IU/mL (p = 0.004)	+	None
			Among breastfed infants, plasma TT ₄ levels at 2 wk inversely associated with breast milk dioxin TEQ (TSH decrement for breast milk dioxin TEQ > 31 vs < 31 pg/g fat)	-18 nM/L	+	None
(Sauer et al. 1994), The Netherlands	Multicentre birth cohort study, 200 mother-infant pairs from large industrial city and 200 from rural region (half were breast-fed and half were formula-fed)	Measured 3 coplanar PCB (77, 126, 169), 23 non-coplanar PCBs and 17 PCDD and PCDF congeners in breast milk; mean breast milk total dioxin-TEQ level (coplanar PCBs, PCDD and PCDFs) was 30 (range 11-76) pg/g milk fat	Maternal plasma TT3 and TT4 were inversely associated with breast milk dioxin-TEQ, coplanar PCBs, non-coplanar PCBs and total TEQ levels (respective Spearman rank correlation coefficients for prenatal maternal TT3 vs breast milk exposure indices)	-0.43, -0.36, -0.40, -0.43 (p < 0.01 for each)	+	None
			Neonatal plasma FT4 and TT4 lower in infants with maternal milk PCB- or dioxin-TEQ above median			None
			Infant plasma TSH levels at age 2 wk and 3 mos were associated with breast milk dioxin-TEQ, coplanar PCBs, non-	0.42, 0.32, 0.36, 0.40 (p < 0.01 for each)	+	None

			coplanar PCBs and total TEQ levels (respective Spearman rank correlation coefficients for infant plasma TSH level at age 3 mos vs breast milk exposure indices)			
(Langer et al. 1998), Slovakia	Cross-sectional study, 454 youth living near former PCB manufacturing plant and 965 youth from 5 less polluted areas, age 17 yr; measured thyroid volume and serum TSH, TT ₄ , thyroglobulin and TSH receptor and urinary iodide	PCB levels elevated in soil and water in contaminated region; previous biomonitoring showed elevated adipose tissue (mean 12.3 µg/g lipid), serum (1.2-9.6 µg/g lipid) and breast milk (1.4 µg/g lipid) PCB levels	Thyroid volume higher in contaminated region compared to control regions	9.4 vs 8.3 ml (p < 0.001)		
			Prevalence of elevated serum TSH levels similar in contaminated and comparison regions	0.8 vs 2.8% (NS)		
(Osius et al. 1999), Germany	Cross-sectional study, 671 children age 7-10 yr (complete data for 320 children); from region potentially exposed to PCBs, lead, cadmium and mercury from a toxic waste incinerator and two comparison regions; measured serum thyroid-stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3)	Measured blood lead (GM 2.7, range 0.5-11.4 µg/dL), cadmium (GM 0.2, range ND-1.8 µg/L) and PCBs (118, 138, 153, 170, 180, 183 and 187) (GM 0.5, range 0.1-4.5 µg/L) and 24-hr urinary mercury (GM 0.15, range ND 12.3 µg/L)	Blood TSH level associated with PCB congener 118 (a dioxin-like congener)	β = 7.1 (p = 0.04)	+	Sex, age, environmental tobacco smoke, fish consumption, blood cadmium and lead, 24-hr urinary mercury
			Blood FT3 level inversely associated with PCB congener 138, 153, 180,	β = -1.0 (p = 0.02)	+	

			183 and 187 levels (β for PCB-138)			
			FT3 inversely associated with sum of 7 PCBs	$\beta = -0.25$ ($p = 0.02$)	+	As above
			TSH not associated with sum of 7 PCBs	$\beta = 0.04$ ($p = 0.79$)		
			No association between blood lead and TSH, FT3 or FT4 levels (respective β coefficients)	$\beta = 0.11, 0.08, -0.13$ (p for each 0.4-0.5)		As above but excluding blood lead
			Blood cadmium associated with TSH and inversely with FT4 (respective β coefficients)	$\beta = 0.71$ ($p = 0.003$) $\beta = -0.51$ ($p = 0.04$)	+	As above but excluding blood cadmium
			Thyroid hormone levels not associated with 24-hr urine mercury	$\beta = 0.18$ ($p = 0.17$)		As above but excluding urinary mercury
(Cheek et al. 1999), New Orleans	<i>In vitro</i> study of interaction of organochlorine compounds with human thyroid receptor (hTR β), transthyretin and thyroid-binding globulin	Tested PCBs, hydroxylated PCBs, DDT and metabolites, acetochlor, alachlor, methoprene	Only hydroxylated PCBs bound to hTR β but with 10,000-fold lower affinity than T3			
		Half of the hydroxylated PCBs had higher affinity than T4 for transthyretin	2 of 7 hydroxylated PCBs bound to thyroid-binding globulin but with 100-fold less affinity than T4			
		DDT and metabolites and chloroacetanilide herbicides did not bind to hTR β	Concluded that PCBs and their hydroxylated metabolites alter thyroid			

			function mainly be competing for serum transport proteins and increasing hepatic T4 metabolism			
(Longnecker et al. 2000), North Carolina	Birth cohort study, 160 mother-infant pairs; measured cord serum TT ₄ , FT ₄ and TSH (TT ₃ results considered unreliable)	Estimated average PCB levels in breast milk at birth (using maternal serum and breast milk levels; adjusted the latter for length of lactation)	Cord serum TT ₄ , FT ₄ and TSH levels not associated with breast milk PCBs in multiple regression analysis			Prenatal maternal smoking, birth weight, race
(Steuerwald et al. 2000), Faroe Islands	Birth cohort study, 182 births at one hospital during 1994-1995; conducted neurologic examination at age 2 wk and derived neurologic optimality scores based on functional abilities, muscle tone, reflexes, responses	Measured mercury in cord blood (GM 20, range 12-40 µg/L) and maternal hair (GM 4.1, range 2.5-7.4 µg/g), PCBs (GM 1.1, range 0.6-1.9 µg/g lipid) and DDE (GM 0.7, range 0.4-1.2 µg/g lipid) in maternal serum, PCBs and DDE in cord serum and breast milk; selenium and thyroid hormones in cord blood, phospholipids in cord serum	Cord blood free T3 inversely correlated with cord serum total PCB levels	r = -0.21 (p = 0.01)	+	
(Nagayama et al. 2001), Japan	Cohort study, 16 Yusho cases, follow-up 30 yr after exposure; measured blood TEQ levels; assessed thyroid and immune function in cases and health comparison group		Except for one elevated T4 level, subjects had normal serum levels of T3, T4, free T4 and TSH			
(Sandau et al. 2002), Canada	Cross-sectional study, 10 neonates in each of 3 regions: a northern coastal area (Nunavik) exposed to PCBs in marine-foods (seal and beluga whale blubber), subsistence	Cord plasma PCP levels were similar in all regions (GM 1670 range 628-7680 pg/g wet weight); cord plasma GM OH-PCB levels among neonates of Gulf of St. Lawrence fishermen and residents	Neonatal cord plasma FT ₄ and T ₃ levels were inversely associated with the sum of cord plasma PCP and OH-PCB levels (respective correlation	r = -0.47 and -0.48 (p < 0.05)	+	

	fishermen on the Gulf of St. Lawrence and Quebec City	of Nunavik and Quebec City were 553 (range 238-1,750), 286 (103-788) and 234 (147-464) pg/g wet weight; corresponding levels of total PCBs were 2,710 (525-7,720), 1,510 (309-6,230) and 843 (290-1,650) pg/g wet weight	coefficients shown)			
			Neonatal cord plasma TSH level was inversely associated with cord plasma PCB and OH-PCB levels (respective correlation coefficients shown)	r = -0.46 and -0.45 (p < 0.05)	+	
Reviews						
(Brouwer et al. 1995), Netherlands	Review of developmental toxicity of PHAHs in experimental animals and infants		Prenatal and lactational exposure to PCBs, PCDDs and PCDFs can cause reduced thyroid hormone levels in humans and experimental animals; these effects have been observed in infants and children exposed to background levels			
(Longnecker et al. 1997), USA	Review of epidemiologic studies of PCBs, DDT and related organochlorines	PCBs and p,p' -DDE comprise the bulk of organochlorine residues in human tissues	The Dutch birth cohort study showed associations between reduced maternal T3 and T4 levels and increased infant TSH levels and background prenatal PCB exposure levels			

			Inconclusive evidence for an association between increased TSH in infants and prenatal dioxin exposure; dioxin and PCB exposure levels were highly correlated, precluding definitive assignment of this apparent effect		
(Brouwer et al. 1998), The Netherlands	Review of health risks to infants of perinatal exposure to PHAHs by a World Health Organization working group		Exposure of rodents to PCB 169 or mixed PCBs during early gestation caused severely reduced fetal and neonatal brain T4 levels		
(Porterfield 2000), USA	Review of literature on potential impact of environmental toxicants on thyroid function and brain development	Perinatal exposure to PCBs and dioxins may exert neurotoxic effects through multiple mechanisms including the Ah receptor and interference with thyroid function	Many PCBs and dioxins have structural similarities to thyroid hormones; hydroxylated metabolites of <i>meta</i> and <i>para</i> PCBs have high affinity for T ₄ -binding proteins such as transthyretin		

Thyroid function: summary

Thyroid function – role of PCBs, dioxins and related compounds

Maternal plasma TT3, TT4, FT4, TSH – Dutch birth cohort studies showed inverse dose-response relationships between prenatal and postnatal maternal plasma TT3 and TT4 levels and breast milk PCB, PCB-TEQ and total dioxin-TEQ levels; maternal plasma FT4 and TSH levels were not associated with breast milk PCB- or total dioxin-TEQ levels (Koopman-Esseboom et al. 1994, Sauer et al. 1994). Longnecker et al. (1997) concluded that there is limited epidemiologic evidence for associations between reduced maternal T3 and T4 levels and background prenatal PCB exposures

Neonatal plasma TT4, FT4, TSH – Breast milk PCB- and total dioxin-TEQ levels were associated with reduced neonatal plasma FT4 and TT4 levels and increased neonatal plasma TSH levels in the larger Dutch study (Sauer et al. 1994) but the North Carolina birth cohort study found no associations between cord

serum TT4, FT4 or TSH levels and breast milk PCB levels (Longnecker et al. 2000). A Faroe Islands birth cohort study found an inverse association between cord blood FT3 and cord serum PCB levels (Steuerwald et al. 2000). A small study of neonates in northern and southern Quebec showed that cord plasma TT3 and FT4 levels were associated with cord plasma pentachlorophenol levels and with the sum of cord plasma pentachlorophenol and hydroxylated PCB levels but not with cord plasma levels of individual or total PCB congeners or total hydroxylated PCBs; neonatal cord plasma TSH levels were *inversely* associated with cord plasma PCB and OH-PCB levels (Sandau et al. 2002). Longnecker et al. (1997) concluded that there is limited epidemiologic evidence for associations between increased infant TSH levels and background prenatal PCB exposures and there is inadequate evidence for an association between infant plasma TSH levels and prenatal dioxin exposure.

Childhood plasma FT3, TSH – A cross-sectional study of children age 7-10 yr living in PCB-contaminated regions in Germany showed that serum FT3 levels were inversely associated with blood levels of individual PCBs (138, 153, 180, 183 and 187) and the total of the 7 PCB congeners measured; serum TSH levels were associated with blood PCB-118 (a dioxin-like congener) levels but not the sum of the 7 PCBs (Osius et al. 1999). A cross-sectional study of older children (age 17 yr) in Slovakia showed similar prevalence rates of elevated serum TSH levels but a higher average thyroid volume among those living in PCB-contaminated compared to unexposed regions (this study did not measure blood PCB levels) (Langer et al. 1998).

Thyroid function – experimental studies of PCBs, dioxins and related compounds

Cheek et al. (1999) found that hydroxylated PCB metabolites bound to human transthyretin *in vitro* with affinities similar to or greater than T4 and to human thyroid receptor and thyroid-binding globulin but with much lower affinities than T3 or T4. The latter study concluded that PCBs and their hydroxylated metabolites alter thyroid function mainly by competing for transthyretin, thereby increasing hepatic T4 metabolism. Other reviewers concluded that (i) prenatal and lactational exposure to PCBs, PCDDs or PCDFs can cause reduced thyroid hormone levels in experimental animals, (ii) early gestational exposure of rodents to PCBs caused severely reduced fetal and neonatal brain T4 levels, (iii) neurotoxic effects of PCBs and dioxins may involve multiple mechanisms including the Ah receptor and interference with thyroid function and, (iv) many PCBs and dioxins have structural similarities to T3 and T4 (Brouwer et al. 1995, Brouwer et al. 1998, Porterfield 2000).

Thyroid function – role of pesticides

Pentachlorophenol – A study of neonates in northern Canada showed inverse associations between cord plasma FT4, T3 and thyroid binding globulin and cord plasma pentachlorophenol levels (Sandau et al. 2002).

DDT, β -HCH – A cross-sectional study of neonates in Spain showed associations between neonatal plasma TSH and cord serum DDE and β -hexachlorocyclohexane levels but not with cord serum hexachlorobenzene levels (Ribas-Fito et al. 2003).

Thyroid function – role of metals

A cross-sectional study of children age 7-10 yr living in PCB-contaminated regions in Germany showed that serum thyroid hormone levels were not associated with blood lead or urinary mercury levels but blood cadmium was associated with decreased FT4 and increased TSH levels (Osius et al. 1999).

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