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## Pesticide Exposure and Health Related Issues in Male and Female Reproductive System

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### 1. Introduction

During the last several decades there have been widespread uses of potent substances that, although effective in their intended use, have also been suspected of being harmful to reproductive health. This mixture of environmental contaminants that may adversely affect human fertility includes heavy metals (lead, mercury, arsenic), phthalates (plasticizers), bisphenol-A (building block of several plastics), polychlorinated biphenyls (lubricants), dioxins (byproducts of manufacture), pesticides and other agents. The impact of adverse effects on reproductive health include impaired gametogenesis, sperm maturation, decreased semen quality, miscarriages, ovulation and menstrual disturbances, infertility, stillbirths, developmental anomalies, cryptorchidism, hypospadias and cancer. The effects can be reversible, permanent or even transgenerational, take place in the offspring, as exposure can occur during pregnancy and intrauterine life, childhood or later. The route of exposure, dose, age, gender and genotype (susceptibility of the individual) are important factors that can determine the reproductive disorder. In this chapter we focus on the effects of exposure to pesticides during adulthood, on human male and female fertility, giving emphasis to semen quality and time to pregnancy.

### 2. Pesticides

Pesticides are mainly utilized in agriculture for crop protection, often replacing the natural processes on which agricultural production had previously depended. Pesticides are also applied in homes and gardens. More than 140.000 tones of pesticides are used annually in the European Union for agricultural purposes only (Ramazzini, 2009).

A pesticide is “any substance or mixture of substances intended for preventing, destroying or controlling any pest, including vectors of human or animal disease, unwanted species of plants or animals causing harm during or otherwise interfering with the production processing, storage, transport or marketing of food, agricultural commodities, wood and wood products or animal feedstuffs, or substances which may be administered to animals for the control of insects, arachnids or other pests in or on their bodies” (FAO, 2003). They

fall into three major classes: insecticides, fungicides, and herbicides, classification based upon the target organism. There are also rodenticides (for control of vertebrate pests), nematicides (to kill eelworms, etc), molluscicides (to kill slugs and snails), and acaricides (to kill mites) (Cox & Sorgan, 2006). Pesticides may differ according to their chemical structure, their mechanism of action and the toxicity they exhibit, but typically each pesticide consists of one (or more) active ingredient, which exerts the pesticidal activity, and an inert ingredient, which is inactive and helps in handling the active ingredient. Several studies have shown that the inert ingredient is not as inactive as it was previously believed to be (Sorgan, 2005; Cox & Sorgan, 2006). Over 700 active ingredients are in use worldwide as pesticides, each with distinct chemical and toxicological properties (Toppari et al., 1996). Another classification categorizes pesticides according their chemical structure (Table 1). Insecticides include organochlorines, organophosphates, and carbamates. Organochlorine hydrocarbons (DDT, heptachlor) operate by disrupting the sodium/potassium balance of the nerve fiber. They are persistent in human tissue with the potential to bioaccumulate. Organophosphate (parathion, malathion) and carbamates (carbaryl, carbofuran) are less toxic and largely replaced organochlorines. They are inhibitors of acetylcholinesterase, causing paralysis. Common herbicides include phenoxy and benzoic acid herbicides (2,4-D) and triazines (atrazine). Fungicides (vinclozolin, mancozeb) have sulfur as the most common active ingredient. Nicotinoids and pyrethroids are plant-derived pesticides (fenvalerate, pyrethrin). In addition to the desired effects of crop protection and pest management, pesticides have some recognized adverse impacts on human health and the environment. Humans have a great risk of exposure through several pathways in occupational, agricultural and household use. Inhalation, oral, dermal and ocular, are four possible routes for pesticide exposure. Ingestion of food and water is thought to be the main routes of pesticide exposure in the general population, while dermal absorption is suspected to be the main source of occupational exposure (Toppari et al., 1996). Over 25% of fruits, vegetables, and cereals are known to contain detectable residues of at least two pesticides and more than 300 different pesticides are known to contaminate food products sold in the EU (Ramazzini, 2009). In the majority of cases, however, human exposure is unintentional and unintended (Ribas-Fitó, 2002).

Pesticides are accused of causing short-term adverse health effects. Acute health effects include stinging eyes, rashes, blisters, blindness, nausea, dizziness, diarrhea and death (Jeyaratnam, 1990; Sanborn et al., 2007). They are suspected also for a wide range of chronic effects, which can occur months or years after the exposure, such as cancers, neurological and developmental toxicity, immunotoxicity, genotoxicity, respiratory effects and disruption of the endocrine system. Pesticides may affect not only the exposed individual but also subsequent generations (Alavanja et al., 2004; Ritter et al., 2006; McCauley et al., 2006; Bassil et al., 2007).

There has been rising concern in many developed countries about the adverse effects of pesticides on human reproduction, ranging from female and male subfertility to abortion, stillbirths, birth defects and malformations (García, 2003; Weselak et al., 2007; Peiris-John & Wickremasinghe, 2008). They may cause reproductive toxicity with direct damage to the structure of the cells or as a result of biotransformation into metabolites, or interference with processes necessary for the natural homeostasis and equilibrium. They may act like hormones in the endocrine system and disrupt the function of the natural endogenous hormones, when doing so they are often called endocrine disrupting chemicals (EDC) (Lathers, 2002; Diamanti-Kandarakis et al., 2009). This group of compounds identified as EDC is heterogeneous and includes synthetic or natural chemicals.

<b>organochlorides</b>	DDD, DDT, DDE, chlordane, kepone, dieldrin, endosulfan, heptachlor, lindane, mirex, methoxychlor, toxaphene
<b>organophosphorus</b>	chlorpyrifos, glyphosate, diazinon, dimethoate, malathion, methamidophos, parathion, terbufos, tribufos, trichlorfon
<b>carbamates</b>	aldicarb, carbaryl, carbofuran, fenoxycarb, propoxur
<b>pyrethroids</b>	cypermethrin, fenvalerate, permethrin, pyrethrin, pyrethrum, resmethrin, tetramethrin
<b>anilides/anilines</b>	metolachlor, pretilachlor, propachlor, trifluralin
<b>phenoxy</b>	2,4-D, 2,4-DB, 2,4,5-T, MCPA, MCPB, fenoprop
<b>triazines</b>	atrazine, cyanazine, hexazinone, prometryn, propazine, simazine, terbutryn
<b>quaternary</b>	diquat, MPP, paraquat
<b>ureas</b>	chlortoluron, DCMU, metsulfuron-methyl, monolinuron
<b>others</b>	acetamiprid, amitraz, chlordimeform, cyromazine, diflubenzuron, nithiazine, sulfuramid, thiachlopid, xanthone

Table 1. Classification of pesticides based on their chemical structure.

### 3. Pesticides as Endocrine Disrupting Chemicals (EDC)

Pesticides may act as endocrine disruptors and alter the hormonal homeostasis in both males and females and lead to subfertility. The term “endocrine disruptors” was introduced into literature with an article published in 1993 (Colborn, 1993). An endocrine disruptor was defined by the U.S. Environmental Protection Agency (EPA) as “an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction and developmental process” (Kavlock et al., 1996). The group of EDC includes pesticides and various synthetic substances such as polychlorinated biphenils (PCB), polybrominated biphenyls (PBB), bisphenol-A (BPA), phthalates and dioxins natural compounds such as phytoestrogens (Fourth National Report on Human Exposure to Environmental Chemicals, 2009) are used as solvents, lubricants, plasticizers, cosmetics etc. They are usually small molecules (mass 1000 Daltons) and often have a phenolic moiety that probably mimics natural steroid hormones (Diamanti-Kandarakis et al., 2009). They contain chlorine or other halogens (bromine, iodine or fluorine) with strong interaction and so they resist degradation. They usually have a long half-life and accumulate in the environment, sometimes remotely from the place they were produced. Substances banned even decades ago can still be found in the environment and in living organisms. In humans and animals EDCs are stored in fatty tissue or they may be metabolized into more toxic compounds. The predominant sources of exposure are food, water and air. The routes of exposure include ingestion, inhalation and dermal absorption.

Natural hormones act in very low concentrations, similarly, can elicit adverse effects in low doses. Occasionally, the EDCs do not follow the classic dose-response effect and low doses may result in stronger effects than high doses (vom Saal et al., 2009). Humans are exposed concomitantly to a large number of compounds. These substances may enhance and have a synergistic or antagonistic effect, and as cited above, some substances can be metabolized in more toxic products (Crews et al., 2003). One of the reasons of the difficulty studying the damage after exposure to a single agent is this mixture of compounds which is accumulated in human organisms.

An issue of critical importance is the timing of exposure, since damage is age sensitive. The same dose can have different effects in fetuses, newborn, infants or adults. Given the same doses, a developing organism (embryo, neonate) whose growth is highly controlled by the endocrine system is more vulnerable to EDCs, than an adult (Guo et al., 1995; Bigsby et al., 1999; Lilienthal et al., 2006). The damage incurred by the exposure may not be immediate and may only be manifested in adulthood or during aging. The consequences may be apparent even in subsequent generations and the classic example is the cases of vaginal carcinoma in daughters of mothers who were exposed to DES during their pregnancies (Herbst et al., 1999; Anway & Skinner, 2006; Rubin, 2007). The susceptibility of an individual may vary due to genetic polymorphism and so the results of the same exposure could be different.

Initially it was thought that EDCs act via nuclear hormone receptors (e.g. estrogen, progesterone, androgen, thyroid receptors), but now it is believed that they act also via membrane, non-steroid receptors (e.g. dopamine, serotonin, nor-epinephrine receptors). Catecholamine hormones following synthesis are stored in granular vesicles intracellularly. Steroid hormones are not stored but readily synthesized following gonadotropin stimulation of the gonads and are usually found in the circulation bound by carrier proteins (only free hormones are biologically active). Once reaching their tissue targets steroid hormones exert their action by binding to different kinds of nuclear receptors. Explicit hormones bind specific receptors and individualized mechanisms follow by intracellular signalling (e.g. protein kinase-C activation or phosphatidylinositol turnover). Hormones are mostly catabolised in the liver. Consequently, EDCs can participate in most aforementioned pathways thereby changing hormone synthesis patterns, mimicking hormone function or blocking it by occupying the receptor site, modulating the number of the receptors and their affinities for specific molecules and altering hormone clearance (Gore et al., 2006; Gore, 2007; Gore, 2008). Sex hormones synthesis is regulated by the hypothalamic-pituitary-gonadal axis. LH and FSH are synthesized by the anterior pituitary under the influence of pulsatile secretion of GnRH, released by the hypothalamus.

Several pesticides have been reported to act as estrogen agonists, e.g. methoxychlor, endosulfan, toxaphene, kepone, DDT, fenarimol, alachlor, pentachlorophenol, fenvalerate, chlordecone (Soto et al., 1995; Cummings & Gray, 1997; Garey & Wolff, 1998; Andersen et al., 2002; Kojima et al., 2004). On the other hand, other pesticides such as vinclozolin, p,p-DDE and o,p-DDT may have anti-androgenic activity, or both estrogenic and antiandrogenic activity (Kelce et al., 1994; Kelce et al., 1995; Kelce & Wilson, 1999). The fungicide methyl-2-benzimidazole carbamate decreases estradiol production in primary cultures of human ovarian granulosa (Can & Albertini, 1997). Treatment of rats with heptachlor suppresses progesterone and estradiol concentrations in blood (Oduma et al., 2006). Progesterone concentrations also decrease during early pregnancy in the rabbit following exposure to the pesticide DDT (Lindenau et al., 1994). DDT was found to be

estrogenic, but its major metabolite DDE, has considerable antiandrogenic activity (Kelce et al., 1995). Further, atrazine seems to have estrogenic and antiandrogenic properties and was suggested to reduce testicular testosterone in male rats exposed to it (Stoker et al., 2000). Lindane intercalates into the sperm membrane and may inhibit sperm responsiveness to progesterone in vitro (Silvestroni & Palleschi, 1999). Lindane also inhibits steroidogenesis by reducing StAR (steroidogenic acute regulatory) protein-mediated cholesterol transfer (Walsh & Stocco, 2000). Neonatal exposure to either DES or flutamide also inhibited steroidogenesis and StAR protein expression in the fetal rat Leydig cell (Mikkilä et al., 2006). This protein mediates cholesterol passage through mitochondrial membranes and impaired expression results in decreased testosterone production in vitro (Manna et al., 2001). Testosterone concentration is also reduced withazole fungicides (ketoconazole) due to impaired enzymatic activity of 17 $\alpha$ -hydroxylase and 17,20-lyase (Wang et al., 1992; Bahshwan et al., 1998; Taxvig et al., 2008). In rats, fenarimol, a different fungicide, was found to cause a dose-related decrease in fertility (Hirsch et al., 1986). In vitro studies of some pesticides such as fenarimol, prochloraz, imazalil and dicofol, indicate these pesticides inhibit the conversion of androgens to estrogens through CYP 19 aromatase inhibition (Vinggaard et al., 2000). Rats treated with mancozeb demonstrate a decrease in the number of healthy follicles and an increase in the number of atretic follicles (Mahadevaswami et al., 2000). EDCs have also been associated with breast cancer, PCO and endometriosis in women, cryptorchidism, hypospadias, testicular and prostate cancer in men, alteration in pituitary and thyroid gland functions (Crisp et al., 1998; Bretveld et al., 2006; Diamanti-Kandarakis et al., 2009).

#### 4. Pesticides and semen quality

Approximately 6% of adult males are thought to be infertile (Purvis & Christiansen, 1992). Male factors are responsible for at least 20% of cases of infertility. Male infertility is related to impaired semen quality and may be due to a variety of causes including genetic (Klinefelter's syndrome), congenital (cryptorchidism), endocrine (hypogonadism), obstructive (vasectomy), infective (chlamydia), vascular (varicocele), neoplastic (carcinoma of the testis), lifestyle, and environmental (heat, drugs, pesticides, irradiation) factors. Others causes include sexual dysfunction related to erection and ejaculation (Purvis & Christiansen, 1992; Dohle et al., 2005). However, in many cases male infertility is regarded as idiopathic (40-75%), and no cause can be identified. Semen analysis is used to evaluate semen quality, which is taken as a surrogate measure of male infertility. The World Health Organization has provided reference values for human semen characteristics (Cooper et al., 2010).

There is evidence of regional variation in semen quality that may be an expression of gene polymorphisms, different climate, lifestyle and exposure to magnetic fields or chemical substances such as pesticides (Mallidis et al., 1991; Jørgensen et al., 2001; Swan et al., 2003; Li et al., 2010). Seasonal variation has also been detected (decrease of sperm density and total sperm count during summer) (Levine, 1999; Krause & Krause, 2002). These factors, together with the variability in techniques and methodologies used, are reasons for some controversial results in studies that analyze semen quality changes overtime. Thus, the issue of a decline in semen quality overtime is equivocal. Following the publication of the meta-analysis conducted by Carlsen et al. in 1992, demonstrating a decline in human semen quality over the last 50 years (mean sperm count from 113 millions/ml in 1940 to 66

millions/ml in 1990), numerous related studies have been published. Studies by Swan et al. had consistent results with those of Carlsen et al. (1992) and supported that historical data on sperm density, despite large random error, are reliable (Swan et al., 1997; Swan & Elkin, 1999; Swan et al., 2000). However, Olsen et al. (1995) reanalyzed the data used in a linear model to predict sperm quality deterioration in the last 50 years, advocate that the data are only robust during the last 20 years (1975-1995), in which other statistical models (quadratic, spline fit and stairstep), except the linear model, suggest constant or slightly increasing sperm counts. Studies from Italy, Denmark, Canada, Tunisia, India, Poland, Israel, Scotland, Greece and Germany suggest that there has been a decline, or sperm parameters are impaired in young populations (Adamopoulos et al., 1996; Younglai et al., 1998; Bilotta et al., 1999; Almagor et al., 2003; Vicari et al., 2003; Jørgensen et al., 2006; Sripada et al., 2007; Adiga et al., 2008; Paasch et al., 2008; Horak et al., 2008; Feki et al., 2009). Conversely, other reports from US, Japan, Korea, Sweden, Spain, Israel and Czech Republic showed no significant evidence of deterioration in sperm quality (Fisch et al., 1996; Paulsen et al., 1996; Benschushan et al., 1997; Berling & Wölner-Hanssen, 1997; Andolz et al., 1999; Seo et al., 2000; Itoh et al., 2001; Zvěřina et al., 2002). The materials and methods of the studies mentioned varied widely, as well as time period (one, two, or more decades), population sample (e.g. individuals in infertile relationship or fertile subjects who participated voluntarily) and the level of pollution in the various geographical regions. Merzenich et al. (2010) conclude that former meta-analyses of sperm count data show a global downward trend, but this conclusion should be interpreted with caution, because the included studies are of great heterogeneity. The geographic variation in semen quality may reflect different exposures to endocrine disruptors, such as pesticides (Swan, 2006). Pesticides might have the ability to interrupt male fertility at several different sites in the reproductive pathway and by one or more mechanisms, as cited previously. Thus, they can interfere with the hypothalamopituitary axis that regulates, through the production of the gonadotrophins FSH and LH, the function of Sertoli and Leydig cells, impairing spermatogenesis and steroidogenesis.

Tables 2a,b,c lists the studies published evaluating the association between exposure to pesticides and human sperm quality. Literature reviews and articles investigating chemical compounds, without including pesticides, were excluded. Studies evaluating pregnancy outcomes and no sperm quality were excluded too. Sperm quality was assessed evaluating conventional parameters (concentration, motility, morphology) or sperm DNA/chromatin integrity and aneuploidy. Sixty-three reports, satisfying these criteria were identified and included in Tables 2a,b,c. Among them six (6/63) studies evaluated the recovery of sperm quality, years after cessation of exposure to DBCP (5) and kepone (1). Thirty-six (36/63) studies examined exposure to single, specific pesticides or metabolites and included DBCP, DDT, DDE, EPB, 2,4-D, kepone (chlordecone), molinate, carbaryl, fenvalerate, ethylparathion, methamidophos, 1N (metabolite of carbaryl and naphthalene), TCPY (metabolite of chlorpyrifos and chlorpyrifos-methyl) and 3PBA, CDCCA, TDCCA (pyrethroid metabolites). The majority of the pesticides cited above are now banned or severely restricted, at least in USA or EU. Twenty-one (21/63) studies evaluated mixture of compounds such as fungicides, insecticides or herbicides with or without specifying the exact pesticides. Some of the pesticides involved in these studies are: alachlor, diazinon, acetochlor, malathion, atrazine, metolachlor, DEET (insect repellent), 2,4-D, aldicarb and cadusaphos, ethoprothos, isazophos, terbufos, pyrimiphos-ethyl (organophosphorus pesticides).

#### 4.1 Studies with little or no evidence of an association

Eighteen studies of the 63 (18/63) found no or little evidence of association between pesticide exposure and sperm quality (Table 2a). Eight studies (8/18) involved a mixture of compounds and ten (10/18) single pesticides. Carbaryl and molinate were reported in one study each. Ten studies (10/18) were related to DDT and metabolites most of the times p,p'-DDE, the known persistent pesticide banned many years ago (not all over the world). Two of the ten studies evaluated DDT in mixtures and eight as a single pesticide. Five (5/10) of the reports that found no or little association between DDT, DDE and semen quality were carried out by the INUENDO project (including the two substudies of INUENDO by Rignell-Hydbom et al. (2004 & 2005). INUENDO (INUit-ENDOcrine) is the acronym for "Biopersistent organochlorines in diet and human fertility. Epidemiological studies in time to pregnancy and semen quality in Inuit and European populations". This EU project (2002-2005) used serum levels of CB-153 (polychlorinated biphenyl) and p,p'-DDE, the main DDT metabolite, to estimate the impact in human fertility in epidemiological studies including Inuits from Greenland and Caucasians from Poland, Sweden and Ukraine. Hauser et al. (2003) conducted two cross sectional studies and found a limited evidence of an inverse association between p,p-DDE and sperm motility as well as no strong relationships between the levels of this compound and sperm DNA damage. Furthermore, Charlier et al. (2005) estimated serum and seminal plasma concentrations of p,p-DDE in fertile and sub or infertile young men. Blood concentrations of p,p'-DDE were very low in both groups. No p,p'-DDE detected in seminal plasma of either groups. Of note, the mothers of the exposed subfertile men had serum level of p,p'-DDE significantly higher than the mothers of the control group.

Two studies did not evaluate DDT exposure separately, but it was included in a sum of other compounds. Magnusdottir et al. (2005) concluded that poor semen quality is associated with sedentary work and obesity but not with plasma levels of fourteen organochlorine pesticides including DDT and metabolites. Weiss et al. (2006) evaluating exposure, in Germany and in Tanzania, to a mixture of PCBs and pesticides, including DDT, found these pesticides had no impact on sperm quality. However high serum concentrations of DDT-DDE were associated with lower pregnancy rates in Germany.

Two out of the eighteen reports that showed little or no association between pesticide exposure and semen quality were performed by ASCLEPIOS (Larsen et al., 1998a; Härkönen et al., 1999). It was an EU project (1993-1998), that was carried out in 14 European centers and focused on occupational exposure to the fungicides styrene and inorganic lead. Questionnaire studies of time to pregnancy were combined with longitudinal and cross sectional studies of semen quality.

Tielemans et al. (1999a) conducted a case-control study and found no associations between exposure to pesticides and poor semen quality, but few subjects were exposed to pesticides (the rest of the sample was exposed to chemical pollutants different from pesticides, such as solvents and metals). Juhler et al. (1999) found similar results indicating minor association, comparing traditional and organic farmers, but for all the groups of exposure the average dietary intake of pesticides was low. Smith et al. (2004) found no significant differences in sperm aneuploidy or diploidy frequencies between men exposed to a mixture of pesticides and control groups, but the sample was rather small (n=20+20). In a cross-sectional study conducted by Multigner et al. (2008) semen characteristics were evaluated in association to exposure to a mixture of organophosphorus pesticides (cadusaphos, ethoprothos, isazophos, terbufos, pyrimiphos-ethyl and one carbamate the aldicarb). No significant difference was



found between exposed and unexposed workers (in banana plantations), but exposure was assessed by a questionnaire and not by chemical analysis. Tomenson et al. (1999) conducted a longitudinal study and found no evidence that sperm and serum hormones levels were related to molinate exposure (thiocarbamate herbicide). Whorton et al. (1979) found no apparent effects on sperm count in workers exposed to carbaryl, but three subsequent relative studies indicated contrary results.

Authors & Year Country	Pesticide	N	Study Type
Whorton et al, 1979 (USA)	carbaryl	47 workers	CS
Larsen et al, 1998a (ASCLEPIOS) (Denmark)	Mixture	248 farmers users or not users of pesticides during a spraying season	L
Härkönen et al, 1999 (ASCLEPIOS) (Finland)	fungicides	30 healthy farmers before and after exposure	CS
Tomenson et al, 1999 (UK)	molinate (thiocarbamate herbicide)	272 workers at three US plants.	L
Tielemans et al, 1999a (The Netherlands)	Occupational exposures (solvents, metals, pesticides)	Male partners of couples having their first consultation in two infertility clinics (n=899)	CC
Juhler et al, 1999 (Denmark)	mixture	171 traditional and 85 organic farmers.	CC
Hauser et al, 2003a (USA)	DDT, DDE, PCBs	212 male partners of subfertile couples	CS
Hauser et al, 2003b (USA)	DDT, DDE, PCBs	212 male partners of subfertile couples	CS
Rignell-Hydbom et al, 2004, (Sweden)	CB-153 p,p'-DDE	195 Swedish fishermen aged 24-65	CS
Smith 2004 et al, (Canada)	mixture	20 exposed, 20 non exposed	CC
Charlier 2005 et al, (Belgium)	p,p'-DDE	73 fertile young men (controls) & 23 mothers; 82 sub or infertile young men (cases) & 19 mothers	CC
Magnusdottir 2005 et al, (Iceland)	PCBs, organochlorine pesticides, (p,p'DDE)	25 poor semen quality, 20 normal semen quality & idiopathic subfertility, 27 normal semen quality & female subfertility	CS
Rignell-Hydbom et al, 2005 (Sweden)	CB-153 p,p'-DDE	176 Swedish fishermen (low & high intake of fatty fish)	CS
Spano 2005 et al, INUENDO, (Italy)	CB-153 p,p'-DDE	193 Inuits - Greenland; 178 Swedish fishermen; 141 men from Poland; 195 men from Ukraine	CS

Stronati et al, 2006, INUENDO, (Italy)	CB-153 p,p'-DDE	200 Inuits -Greenland; 166 men from Sweden; 134 men from Poland; 152 men from Ukraine	CS
Toft et al, 2006, INUENDO, (Denmark)	CB-153 p,p'-DDE	194 men from Greenland; 185 men from Sweden; 189 men from Poland; 195 men from Ukraine	CS
Weiss et al, 2006 (Germany)	mixture of PCBs & pesticides including DDT,DDE	31 women, 16 men from Tanzania, 21 couples from Germany	CS
Multinger et al, 2007 (France)	organophosphorus pesticides and one carbamate	42 exposed & 45 non exposed in banana plantations in Guadeloupe (parallel assessment in wild rats)	CS

Table 2a. Studies evaluating the association between exposure to pesticides and human sperm quality. Studies with no or little evidence of an association; 2b: Studies with evidence of an association; 2c: Studies evaluating the recovery of sperm quality (CS: cross sectional study; CC: case-control study; L: longitudinal study; R: retrospective study; P: pilot study).

#### 4.2 Studies with evidence of an association

Thirty-nine (39/63) studies that varied widely in materials, methods, exposure and assessment of exposure concluded that there was evidence of an association between exposure to pesticides and impaired semen quality. Twenty-six (26/39) studies evaluated exposure to single pesticides or metabolites and thirteen (13/39) studies evaluated exposure to mixtures of compounds including pesticides or mixtures of pesticides. Evidence of an association was found in studies involving:

- DDT and DDE: Only in six of the 16 studies overall involved, five as a single pesticide and one in a mixture.
- DBCP: All studies showed evidence of impairment. Thrupp in his article examined a remarkable case of massive sterilization of approximately 1500 workers exposed in banana plantations in Costa Rica (Thrupp, 1991). Slutsky et al. in his report which represents the largest cohort of DBCP exposed workers, found that after a median exposure of three years, 64.3% of these men overall, and 90.1% of men studied from the Philippines, had oligospermia or azospermia (1999). Whorton et al. (1977), Potashnik et al. (1978), Lipshultz et al. (1980) and Egnatz et al. (1980) had the same results of a significant association. There are five studies more involving DBCP, but related to sperm recovery after cessation of exposure and are cited in the related paragraph.
- EPB: One cross-sectional and one longitudinal study with small sample size.
- Kepone: A cross-sectional study measuring blood levels found oligospermia and decreased sperm motility. One more study involving kepone was related to the recovery of sperm after exposure and is cited in the related paragraph.
- 2,4-D: One cross sectional study evaluated exposure using urine samples and observed asthenospermia, teratospermia and necrospermia. The second study evaluated this compound in a mixture of eight pesticides and found relation with poor semen quality.
- Fenvalerate: All studies conducted in China; three of them reporting impairment of conventional parameters of sperm quality and one increased percentage of sperm aneuploidy and altered morphology.

- Carbaryl: The first, a cross-sectional study, showed increase in abnormal morphology, the second study found altered seminal volume and sperm motility and the third study showed increased frequencies of aneuploidy.
- Ethylparathion and Methamidophos: Semen and urine samples were collected in order to estimate exposure to these organophosphate pesticides. There was a decrease in sperm concentration and motility but no significant difference was found in sperm morphology.
- 1N and TCPY: The first compound is a metabolite of carbaryl and naphthalene and the second a metabolite of chlorpyrifos and chlorpyrifos-methyl. This study used biological markers of exposure (urine analyses for metabolites) and several modeling approaches to test the robustness of the data. Statistically significant inverse dose- response relationships between 1N and sperm concentration and motility were found. There was a suggestive association between TCPY and sperm concentration and motility. Sperm morphology was not significantly associated with both 1N and TPCY. Only a single urine sample collected to estimate exposure and only a single semen sample collected to assess semen quality.
- 3PBA: It is the main metabolite of pyrethroids such as cypermethrin, deltamethrin, permethrin with high detection rate in the general population. The first study with rather large sample size showed suggestive association between increased urinary 3-PBA concentration (creatinine adjusted) and sperm concentration. There was an association between straight line velocity and curvilinear velocity (sperm progression and motion parameters) with urinary 3-PBA concentration (creatinine adjusted), while sperm volume, sperm number per ejaculum and sperm motility were weakly or not significantly associated. A second study that evaluated two more pyrethroid metabolites, CDCCA and TDCCA, was similar in design and found evidence for reduced semen quality and increased DNA damage related to the urine pyrethroid metabolites. Swan et al. (2003b) evaluated exposure to a mixture of eight pesticides in two different populations within Missouri and Minnesota. The small sample size limited statistical power. Exposure was assessed by urine analysis. Study concluded that Alachlor, atrazine, 2,4-D, metolachlor and a diazinon metabolite were associated with poor semen quality in Missouri. However, no significant associations were found for acetochlor, DEET and malathion dicarboxylic acid. Within Minnesota, the levels of pesticides were low for any of the pesticides, no significant associations were found too, but because of the overall results this study is classified in this category.

Dalvie et al. (2004) evaluated exposure to DDT in workers in South Africa, in relation to sperm quality and sexual function. Exposure was assessed by serum levels of *o'p'* and *p'p'* isomers of DDT, DDE, DDD. Sperm count and density were in the normal range. 84% of morphology scores were below the WHO criteria and *p'p'*DDT was negatively associated with sperm count (after correction for age, abstinence, physical abnormality and fever). Although no strong evidence for a DDT overall effect in sexual function and reproductive outcomes was found semen quality was impaired resulting in this study being cited in this category.

Dallinga et al. (2002) studied a group of men with poor semen quality vs. group of men with normal, based on the progressive motility of sperm. Blood samples were collected in order to determine whether differences in sperm quality were related with differences in serum concentrations of organochlorines, including DDT. No significant differences in

organochlorine levels were found initially, but after adjustment for age and sperm count, sperm progressive motility were inversely related to the concentrations of metabolites in the group of men with normal semen quality. Because of this finding the study is cited in this category.

Authors & Year Country	Pesticide	N	Study Type
Whorton et al, 1977 (USA)	DBCP	25 workers	CS
Cannon et al, 1978 (USA)	kepone	133 workers	CS
Potashnik et al, 1978 (Israel)	DBCP	6 workers	CS
Lipshultz et al, 1980 (USA)	DBCP	228 workers (exposed & non exposed cohort)	CS
Egnatz et al, 1980 (USA)	DBCP	232 workers exposed, 97 workers non exposed	CS
Wyrobek et al, 1981 (USA)	carbaryl	50 men occupationally exposed, 34 unexposed newly-hired	CS
Henderson et al, 1986 (Australia)	Mixture of chemicals including pesticides	1695 men with abnormal semen quality or fertility impairment	CS
Ratcliffe et al, 1987 (USA)	EDB	46 exposed in papaya fumigation industry in Hawaii; 43 unexposed from a sugar refinery.	CS
Schrader et al, 1988 (USA)	EDB	10 exposed forestry employees, 6 unexposed (exposing time 6 wks)	L
Thrupp et al, 1991 (USA)	DBCP	exposed workers in a banana plantation in Costa Rica	L
Lerda et al, 1991 (Argentina)	2,4-D	32 farm sprayers	CS
Strohmer et al, 1993 (Austria)	mixture	101 couples seeking artificial insemination (poor semen quality), controls couples with female infertility IVF treated	CS
Slutsky 1999 et al, (USA)	DBCP	26400 workers in banana & pineapple plantation in 12 countries	R
Abell et al, 2000 (Denmark)	mixture	122 greenhouse workers	CS
Padungtod et al, 2000 (USA)	Ethylparathion Methamidophos	32 exposed workers & 43 not exposed workers in China factories	CS
Ayotte et al, 2001 (Mexico)	DDT P,P'-DDE	24 Mexican men living in endemic malaria areas not occupationally exposed	CS
Oliva et al, 2001 (Argentina)	mixture of pesticides & solvents	225 male partners from infertility clinics	CS

Dallinga et al, 2002 (The Netherlands)	Organochlorine compounds PCBs, HCB, p,p'-DDT, p,p'-DDE	34 men with poor semen quality vs. 31 men with normal (based on progressively motile sperm concentration)	CS
Tan et al, 2002 (China)	fenvalerate	32 exposed workers, 46 administrators (internal control group), 22 administrators (external control group)	CC
Swan et al, 2003b (USA)	8 metabolites of pesticides (alachlor, diazinon, acetochlor, metolachlor, 2,4-D atrazine, DEET, malathion)	Men in whom all semen parameters were low (cases) or within normal limits (controls), in Missouri & Minnesota (50 & 36 respectively)	CC
Wong et al, 2003 (The Netherlands)	Chemicals including pesticides & other factors	73 subfertile & 92 fertile men	CC
Bian et al, 2004 (China)	fenvalerate	21 exposed workers, 23 non exposed workers (internal control group), 19 non exposed workers (external control group)	CC
Dalvie et al, 2004 (South Africa)	DDT, DDE	60 workers in South Africa	CS
Kamijima et al, 2004 (Japan)	Organophosphorus & pyrethroid insecticides	18 male sprayers, 18 age matched students or medical doctors as unexposed controls	L
Meeker et al, 2004 (USA)	1N (a metabolite of carbaryl & naphthalene), TCPY (a chlorpyrifos & chlorpyrifosmethyl metabolite)	272 men recruited through a Massachusetts Infertility clinic	CS
Pant et al, 2004 (India)	DDT, DDE, DDD, HCH	45 fertile & 45 infertile men	CS
Sánchez-Peña et al, 2004 (Mexico)	mixture of organophosphorus pesticides	33 men occupationally exposed (initially 227)	CS
Xia 2004 (China)	Fenvalerate	12 exposed workers, 12 internal control group, 18 external control group	CC
Xia et al, 2005 (China)	carbaryl	16 exposed workers, 12 internal control group, 18 external control group	CC
Tan et al, 2005 (China)	carbaryl	31 exposed workers, 46 internal control group, 22 external control group	CC

De Jager et al, 2006 (Canada)	DDT p,p'-DDE	116 men aged 27 years, non occupationally exposed living in malaria, endemic areas in Mexico	CS
Lifeng et al, 2006 (China)	fenvalerate	32 exposed workers, 46 internal control group, 22 external control group	CC
Yucra et al, 2006 (Peru)	Organophosphate pesticides	31 pesticide sprayers, 80 not exposed men	CS
Aneck-Hahn et al, 2007 (South Africa)	DDT p,p'-DDE	311 healthy men 18-40 years in an endemic malaria area in which DDT is sprayed (non occupational exposure)	CS
Perry et al, 2007 (USA)	organophosphorus & pyrethroid insecticides	18 males of reproductive age in China	P
Tuc et al, 2007 (Thailand)	Mixture	1036 rice farmers: 156 of these with abnormal semen & 314 with normal semen (as controls)	CC
Meeker et al, 2008 (USA)	Metabolites of pyrethroid insecticides: 3PBA, CDCCA, TDCCA	207 men recruited from an infertility clinic	R CC
Recio-Vega et al, 2008 (Mexico)	Organophosphorus pesticides	52 men in three occupational exposure levels	L
Xia et al, 2008 (China)	3-PBA (urinary metabolite of pyrethroids)	376 men with non obstructive infertility	R CC

Table 2b. Studies evaluating the association between exposure to pesticides and human sperm quality. Studies with evidence of an association (CS: cross sectional study; CC: case-control study; L: longitudinal study; R: retrospective study; P: pilot study.)

#### 4.3 Studies evaluating the recovery of sperm quality

There are six (6/63) studies, evaluating the recovery of sperm quality, years after cessation of exposure to DBCP and kepone (five and one study respectively). In 1986 Eaton et al. conducted a follow-up study among 44 male agricultural workers who were exposed to DBCP years ago. These workers were found to be azoospermic or oligospermic due to DBCP exposure in a previous study and their sperm was reevaluated 5 to 8 years after exposure was terminated. Only 2 of the 8 originally azoospermic workers produced sperm during the follow up and only one had normal sperm count. There was no increase in sperm production for the oligospermic men. Authors suggested a permanent destruction of germinal epithelium. Potashnik et al. conducted two follow-up studies evaluating 15 DBCP production factory workers (Potashnik & Yanai-Inbar, 1987; Potashnik & Porath, 1995). The reports reassessed their testicular function and reproductive performance, 8 and 17 years after cessation of exposure. The first study showed recovery of spermatogenesis in 4 oligo- and 3 azoospermic men, while testosterone levels of all patients were normal at all times.

The second follow up showed a significant increase in plasma FSH and LH levels in the severely affected men and no increase in the rate of spontaneous abortions or congenital malformations among pregnancies conceived during or after exposure. Recovery was evident in three of the nine azoospermic men and in three of the six oligospermic men. Olsen et al. (1990) conducted a follow-up study among azoospermic and oligospermic workers who had a maximum of 18 months of DBCP exposure. After an 11-year period, 73% of the previously azoospermic showed recovery of spermatogenesis; 13 of the men had normospermic levels and normospermic levels were found among all of the previously oligospermic men (17/17). Another study was undertaken by Lantz et al. (1981), among 14 oligospermic workers who had a maximum of 30 months of DBCP exposure. Follow up (18-21 months) showed an increase in sperm count suggesting that there is a recovery after a short term exposure. In a cross-sectional study conducted in 1982 Guzelian treated oligospermic patients who had high serum levels of chlordecone (0.6-32.0 µg/g) with cholestyramine, an anion-exchange resin. Cholestyramine binds chlordecone and increases its fecal excretion by seven-fold, resulting in reduction of chlordecone blood levels. The author found sperm motility restoration after treatment and suggested this indicated reversibility of the results.

Authors & Year Country	Pesticide	N	Study Type
Lantz et al, 1981 (USA)	DBCP	14 oligospermic workers	L
Guzelian et al, 1982 (USA)	kepone	13 workers highly exposed	CS
Eaton et al, 1986 (USA)	DBCP	44 workers 7 years after termination of exposure	L
Potashnik et al, 1987 (Israel)	DBCP	15 workers with DBCP induced azoospermia & oligospermia, 8 years after exposure.	L
Olsen et al, 1990 (USA)	DBCP	26 azoospermic and 17 oligospermic men with a maximum of 18 months of exposure	L
Potashnik et al, 1995 (Israel)	DBCP	15 workers with DBCP induced azoospermia & oligospermia, 17 years after exposure.	L

Table 2c. Studies evaluating the association between exposure to pesticides and human sperm quality. Studies evaluating the recovery of sperm quality. (CS: cross sectional study; L: longitudinal study)

#### 4.4 Comments

The studies evaluating pesticide exposure and sperm quality were usually cross sectional. This design is relatively inexpensive and can be conducted over a short period of time. However, inherent to the study design, it is difficult to separate cause from effect, because the measurement of exposure and the possible health impairment are conducted the same simultaneously. Thus if the effect takes place later on in life, it may be misevaluated and critical windows of exposure (intrauterine, neonatal and early adulthood life) are not considered adequately.

The studies involving sperm collection have low participation rate and this, in combination with small sample size, decreases statistical power. Men providing sperm for analysis are usually self-selected volunteers that may have concerns about their fertility and this may influence the results of semen characteristics. Some embarrassment associated with sperm collection results in men who are considered fertile to be less likely to participate in such studies (selection bias). Exposure assessment in half of the reports was performed without using specific chemical analyses. Modern studies provide more accurate estimations of exposure measuring the exact levels of contaminants in humans, although there is a certain limitation regarding non-persistent pesticides that are metabolized and excreted relatively fast. Very recent studies, using biological monitoring of exposure, evaluate the susceptibility of individuals after pesticide exposure and demonstrate that genetic polymorphism modifies exposure effects on semen quality (Pérez-Herrera et al., 2008). Many of the studies that showed no or little association of exposure to pesticides and semen quality come from the north of Europe. Maybe the cumulative exposure to pollutants in this geographic area is limited compared to others. Following the evaluation of the above epidemiological studies, we conclude that overall there is suggestive evidence of an association between pesticide exposure and semen quality.

## 5. Pesticides and time to pregnancy

Baird et al. (1986) proposed “time to pregnancy” (TTP) as a simple measure in epidemiological studies to investigate the effects of environmental exposures on reproduction. Time to pregnancy is defined as the time interval (number of menstrual cycles, expressed in months) between the start of unprotected intercourse and a clinically recognizable pregnancy. Fecundability is defined as the probability of conception for each menstrual cycle and varies among sexually active couples not using any contraception method. The fecundability of a couple is estimated by the inverse of time to pregnancy (time to pregnancy =  $1/\text{fecundability}$ ). TTP does not consider the exact biological pathways (including gametogenesis, fertilisation, transport and implantation of the zygote, early survival of the conception product) or mechanisms involved in human fertility. Semen quality impairment, discussed earlier, is not a direct parameter of fecundity and altered semen quality does not necessarily entail changes in TTP (Joffe, 2000). TTP appears to be a non expensive, easy-to-determine indicator (obtained by questionnaires and interviews) and a sensitive measure of fecundability in either sex (Joffe, 1997).

The evaluation of pesticide effects on fecundability using TTP could be considerably susceptible to bias as highlighted by the following discussion. TTP studies are usually retrospective and based on questionnaires and interviews, susceptible to selection, response and recall bias. Individuals that have encountered problems of infertility or subjects occupationally exposed may not have the same response to participate in related studies, compared to fertile or unexposed population. Questionnaires may concern pregnancies that occurred several years back and require the recall of events that are not well remembered. Low participation rates and small sample size may limit the statistical power of the study. Time-trend bias may be prominent if the exposure under study has changed over time. TTP studies concern planned pregnancies and fertile couples with unwanted, mistimed or because of contraception failures pregnancies are more likely to be excluded (planning bias). Because of censoring prolonged time to pregnancy period (12 months for the majority of the



studies), subfertile couples who need periods longer than 12 months to have conceive are underestimated and infertile couples are excluded (sterility bias). On the other hand couples who are in search of assisted reproduction programmes or benefit from a therapeutic effect of a treatment, after a long waiting period, are not included. It often difficult to recognize early fetal loss, therefore, early spontaneous abortions may lead to an overestimation of TTP. Studies that are not limited to first pregnancy may be biased by the “reproductively unhealthy worker effect”: fertile women might be more likely to have children, spend their time taking care of them, or having part time jobs and as a result be less occupationally exposed. Most of the TTP studies do not assess exposure by directly measuring the concentrations of pollutants in human tissues or liquids. Usually, exposure is evaluated by the same questionnaires and interviews used to estimate TTP (self-reported data), which is simple and not expensive, but inaccurate, even if the questionnaires are detailed (specific pesticides mentioned, exact hours of spraying, quantity of pesticides applied, methods of application, protective equipment used, etc). Biological monitoring seems to be a better method to evaluate exposure, despite some limitations. The measurement of non persistent pesticides concentrations in humans cannot always reflect exposure in the time to pregnancy period accurately, as they are excreted in a relatively short period of time and many pesticides cannot be measured in biological matrices (Bradman & Whyatt, 2005). Important potential confounders that have to be taken into account include: age, ethnicity, parity, previous contraceptive use, medical conditions, and frequency of intercourse, BMI, breastfeeding, smoking, caffeine and alcohol consumption.

Table 3 shows the 29 studies that evaluate exposure to pesticides and time to pregnancy. Among these studies, three studies estimate fertilization rates and time to cleavage in women attending IVF programmes, and three studies evaluate fecundity relative to dietary intake of contaminated fish. The results are conflicting, perhaps because of the heterogeneity of study design and misclassification of exposure. The only pesticides evaluated as single pesticides and not in mixtures were glyphosate (one study), and DDT and metabolites (four studies). Some of the pesticides included in mixtures were: abamectine, imidacloprid, methiocarb, pirimicarb, deltamethrin, acephate, methomyl, cyromazine, propoxur, hexaflumuron, dichlorvos (insecticides), metalaxyl, captan, procymidon, pyrazophos, toclofosmethyl, zineb, benomyl (fungicides), acrinathrin, propargite (acaricides). DDT, DDE, HCB (hexachlorobenzene), trichlorobenzene, tetrachlorobenzene, lindane, heptachlor, aldrin, chlordane, oxychlordane, endosulfan, methoxychlor, mirex were the organochlorine pesticides most commonly used.

Sanin et al. (2009) found that reduced fecundability in some regions was not associated with the use of glyphosate. DDT and metabolites were involved in four studies as a single pesticide. Toft et al. (2005), INUENDO group, showed that fecundability is inversely related with serum concentration of p,p'-DDE. Cocco et al. (2005) concluded that the fecundity ratio among spouses of DDT applicators compare to the unexposed was decreased, but the low statistical power of the study did not allow definitive conclusions. Cohn et al. (2003) measured serum levels of DDT and DDE in mothers and evaluated TTP in their daughters. Daughters' probability of pregnancy fell by 32% per 10µg/L p,p'-DDT in maternal serum, but increased 16% per 10µg/L p,p'-DDE. Axmon et al. (2006), in a big study of INUENDO, evaluating exposure to CB-153 (biphenyl) and p,p'-DDE found no effect on TTP of either male or female exposure in Sweden, Poland and Ukraine. In Greenland there seemed to be an association, but it was not possible to determine if it was due to CB-153 or p,p'-DDE.

Four studies evaluated DDT and its metabolites in mixtures. One found decreased fecundity related to exposure (Gerhard et al., 1999) and three of the studies indicated no significant association (Law et al., 2005; Axmon et al., 2006; Harley et al., 2008). Two studies examined DDE exposure in women undergoing IVF with contrary results (Jarrell et al., 1993; Younglai et al., 2002). Three studies evaluated fecundity in relation to dietary intake of contaminated fish (Courval et al., 1999; Axmon et al., 2000; Buck et al., 2000). The first suggests a modest association for men only. The second resulted in a negative association between exposure to persistent organochlorine compounds and fertility among heavy smokers and the third concluded that maternal consumption of contaminated fish may reduce fecundability. Three studies overall, evaluated the association between pesticide exposure and fertilization rates, in women attending IVF. Tielemans et al. (1999b) found an association, but exposure was assessed by questionnaires and interviews. Jarrell et al. (1993) had contrary results, but there were trace amounts of contaminants in the follicular fluid. The study conducted by Younglai et al. (2002) did not show any significant association, except for p,p'-DDE, which was associated with failed fertilization.

Curtis et al. (1999) found no significant or consistent pattern of associations between time to pregnancy and pesticides. However 6 of 13 pesticide categories were associated with decreased fecundability, during the exposure periods in which women and most of the men participated in pesticide-related activities. In a prospective study, Sallmen et al. (2003) illustrated a significant association for pyrethroids and suggestive association for carbamates and organophosphates. Restricting analyses for the first pregnancy only, a prolonged TTP was found among male and female greenhouse workers (Bretveld et al., 2006; Bretveld et al., 2008a & 2008b). According to Harley et al. (2008) prolonged TTP was related to maternal occupational pesticide exposure, home pesticide use and residence within 200 feet of an agriculture field. There was no relation with paternal occupational exposure (assessed by maternal interviews) and DDT and DDE (levels measured in maternal serum). Cole et al. (2006) using biological monitoring of exposure found that factors associated with prolonged TTP in multivariate analysis were high caffeine consumption and maternal mercury serum level. Among several pesticides analyzed, only higher maternal benzene hexachloride levels in bivariate analysis were related with prolonged TTP. However, the sample size of this study was small.

De Cock et al. (1994), Fuortes et al. (1997), Abell et al. (2000), Petrelli et al. (2001) and Idrovo et al. (2005) showed an association between impaired fecundity and exposure to pesticides, while Heacock et al. (1998), Larsen et al. (1998b), Thonneau et al. (1999), Law et al. (2005) and Lauria et al. (2006) found insignificant effects. Overall 11 studies showed an association between pesticide exposure and prolonged TTP or decreased fecundity, 7 studies found a rather inconclusive or insignificant association and 11 studies had results that are more complex to interpret and difficult to be categorised in the two groups cited above. Twenty (20/29) studies used retrospective design and only nine (9/29) used biological monitoring of exposure. Even among the studies that used biological assessment of exposure, results are conflicting. Analyses of pollutants in human tissue and liquids give important and accurate information about the cumulative exposure of an individual but there is a lack of information about timing of exposure, which may be critical for the manifestation of a reproductive impairment, such as subfecundity. Moreover, the synergistic effect of pollutants and individual susceptibility to harmful agents are factors that are difficult to estimate.

Authors & Year Country	Pesticide	N	Stuy Type
Jarrell 1993 <i>et al</i> , (Canada)	chlordan, HCB, DDE, epoxide-oxychlordane, PCB	74 women undergoing IVF	CS
De Cock 1994 <i>et al</i> , (The Netherlands)	mixture	43 fruit growers, (91 pregnancies)	CS
Fuortes <i>et al</i> , 1997 (USA)	Agriculture related exposures including pesticides	281 infertile women (cases), 216 postpartum women (controls)	CC
Heacock <i>et al</i> , 1998 (Canada)	Chlorophenate. fungicides	26487 sawmill workers, 23829 exposed, 2658 unexposed	R
Larsen <i>et al</i> , 1998b ASCLEPIOS, (Denmark)	mixture	450 traditional farmers spraying pesticides, 72 traditional not spraying, 94 organic not exposed	R
Courval <i>et al</i> , 1999 (USA)	mixture, including pesticides (dietary intake of sport fish)	626 couples (anglers)	R
Curtis <i>et al</i> , 1999 (USA)	mixture	1048 farm occupants, 2012 pregnancies	R
Gerhard <i>et al</i> , 1999 (Germany)	chlorinated hydrocarbons (CHC) (including pesticides)	489 infertile women	CS
Thonneau <i>et al</i> , 1999 ASCLEPIOS (France)	mixture	142 rural exposed workers and 220 not exposed (France); 326 exposed and 123 not exposed farmers (Denmark); 121 greenhouse workers exposed (Denmark)	R
Tielemans <i>et al</i> , 1999b (The Netherlands)	mixture	836 couples who sought in IVF treatment; 20 men exposed - 816 reference group	CC
Abell <i>et al</i> , 2000b (Denmark)	mixture used in greenhouses	492 pregnancies of women employed when they stopped contraception to have a child (starting time)	R
Axmon <i>et al</i> , 2000 (Sweden)	Organochlorine compounds dietary intake of fatty fish	Fishermen's wives from the Swedish east (n=399) and west coasts (n=936)	R
Buck <i>et al</i> , 2000 (USA)	mixture, including pesticides (dietary intake of sport fish)	895 women after years of fish consumption from lake Ontario	R
Petrelli <i>et al</i> , 2001 (Italy)	mixture of pesticides	127 greenhouse workers 173 clerical workers	R
Younglai <i>et al</i> , 2002 (Canada)	mixture of compounds including pesticides	21 couples attending IVF programme	CS
Cohn <i>et al</i> , 2003 (USA)	p,p'DDT, p,p'DDE	preserved maternal serum (n=289)	R

Sallmen et al, 2003 (Finland)	mixture	578 couples, Finnish green house employers and employees	P
Toft et al, 2005 INUENDO (Denmark)	CB-153 p,p'DDE	Poland: 472 women, 198 male spouses; Ukraine: 640 women, 208 male spouses; Greenland: 598 women, 201 male spouses; Sweden: 559 women, 191male spouses	R CS
Cocco et al, 2005 (Italy)	DDT	spouses of 105 men exposed	R
Idrovo et al, 2005 (Colombia)	mixture of pesticides including thiocarbamates (propineb, mancozeb)	2085 women working in cut flower production	CS R
<i>Law et al, 2005 (USA)</i>	PCBs, DDE	390 pregnant women enrolled at 12 study centers in US between 1959-1965 (before PCBs or DDE was banned in US)	R
<i>Axmon et al, 2006 INUENDO (Sweden)</i>	CB 153 p,p'-DDE	778 men, 1505 women (couples from Greenland, Poland, Ukraine & a cohort of Swedish wives)	R
Bretveld et al, 2006 (The Netherlands)	mixture of pesticides	398 female greenhouse workers - 524 referents	R
<i>Cole et al, 2006 (Canada)</i>	Mixture (metals, PCBs, organochlorine pesticides)	41 couples having their first pregnancy	R
<i>Lauria et al, 2006 (Italy)</i>	mixture	713 female greenhouse workers	R
Bretveld et al, 2008a (The Netherlands)	mixture	694 greenhouse workers exposed, 613 unexposed reference group	R
Bretveld et al, 2008b (The Netherlands)	mixture	101 couples with female greenhouse workers, 957 couples with male greenhouse workers; 1408 referents	R
Harley et al, 2008 (USA)	mixture of pesticides, DDT, DDE	402 pregnant women living in a farmworker community; in 289 of them DDT and DDE serum levels measured.	CS
<i>Sanin et al, 2009 (Mexico)</i>	Glyphosate (herbicide)	2592 fertile Colombian women from 5 regions with different exposure	R

Table 3. Studies evaluating exposure to pesticides and time to pregnancy. In italics: Studies that reveal no association. (CS: cross sectional study; CC: case-control study; L: longitudinal study; R: retrospective study; P: prospective study.)

## 6. Conclusive remarks

It is challenging to estimate if exposure to pesticides has harmful effects on human fertility, because there are many factors that can influence, limit or bias the results of the studies related to fertility. There are two main issues that have to be considered: the methods used to estimate fertility and accuracy of exposure assessment. Related epidemiological studies use basically two methods of fertility evaluation, the semen quality analysis, which is a surrogate and is indirect, and TTP assessment, which is considerably susceptible to bias. As cited before, fecundity is the important parameter that we have to study and that is the capability of producing offspring and not the actual production (fertility). Fertility rates are increasing in developed countries but this is not a proof that fecundity is increasing too. In actuality, human fecundity seems to be decreasing. Fertility rates are influenced by many factors such as socioeconomic status, immigration, health condition and medical service, the practice of contraception and abortion, the sexual behaviour and frequency of intercourse, the methods of assisted reproduction. Given the influence of age on female fecundity, the effects of the baby boom generation, the evolution of the two-child family and the trend for marriage and childbearing later on in life, a decline in fecundity would be expected.

The decline in semen quality overtime is still equivocal, perhaps because the standard assessments (count, motility and morphology) are insufficient. It is interesting that documented changes in semen quality are not always correlated with parallel changes in TTP. In the future, consideration of additional parameters of sperm quality that provide information about the sperm-egg binding event would be helpful. Modern techniques employed to evaluate DNA damage in spermatozoa such as single cell gel electrophoresis (COMET assay), Terminal transferase dUTP Nick End Labelling (TUNEL), sperm chromatin structure assay (SCSA), in situ nick translation (ISNT) as well as and sperm aneuploidy (FISH) have to be incorporated in future studies.

Pesticides are endocrine disrupting chemicals warranting research to elucidate their mechanisms of action. Timing of exposure is critical, as the same dosage seems to have diverse effects in individuals of different age and exposure in critical windows of development (intrauterine life, neonatal period, childhood) seems to be more harmful. The classical dosage-effect rule of toxicology is contradicted by some EDCs and low doses may damage more than high doses. Individuals are often exposed to a mixture of toxicants, not a single agent, and the effects may be synergistic or antagonistic. The results of an exposure may be apparent immediately but can also become apparent on at a later stage and sometimes in subsequent generations, with varying susceptibility that may depend on genetic polymorphism. Often, studies requiring semen collection have low participation rates and thus the men providing sperm for analysis are usually self selected volunteers that may have concerns about their own fertility and may not be a true reflection of the general population. Geographical and seasonal variation of semen parameters make results difficult to compare. Most of the epidemiological studies reporting chemical exposure and semen quality damage are cross-sectional. In this design, the measurement of exposure and the possible health impairment are conducted simultaneously and, because of the factors cited above, results can be easily biased. A need for a longitudinal design in studies of semen quality is apparent.

TTP studies are usually retrospective. TTP estimation and exposure assessment are carried out using questionnaires and interviews, a method relatively inexpensive, but not precise. Unplanned pregnancies are not included in TTP studies. Therefore, fertile couples, because

of mistimed, unwanted or contraceptive failure pregnancies are excluded. A percentage of early fetal losses is not recognised and not included in these studies. Subfertile couples are underestimated because of censoring prolonged time to pregnancy to a period of around 12 months. Fertile women might be more likely to have children and be less busy in occupational activities and therefore less occupationally exposed (reproductively unhealthy worker effect). Restricting TTP studies for women attending only their first pregnancy is required. A prospective design that recruits couples early at the beginning of their attempt at a pregnancy, with more than one chemical analyses of specific pollutants per individual, during study period, might be less susceptible to bias and give more concrete results. In the majority of the studies cited above, exposure was evaluated by a simple questionnaire. There are few studies that directly measure the concentration of a toxicant in human tissue or liquids. Precise measurements of follicular fluid are more difficult to obtain. Biological monitoring is more precise, although with certain limits for non persistent pesticides and for the estimation of the primary source of exposure, since cumulative levels of pollutants are measured.

In evaluating epidemiological studies of exposure to pesticides and human semen quality, there is suggestive evidence of an association between exposure and semen quality impairment. The evaluation of the scientific literature related to human pesticide exposure and TTP results are conflicting. However, research results in animal and in vitro studies are clear and suggest that pesticides can adversely affect fertility. Unfortunately, these results cannot be taken as proof for humans strong enough to stop or modulate pesticide production. In the future, pesticides might be less toxic and it will therefore be even more difficult to estimate their adverse effects in human fertility. The evidence for impaired fecundity is strong in both in vivo and in vitro studies and investigators have to cooperate in order to optimise the research and raise public awareness and concern. Therefore, scientists need to emphasize the need for stricter rules dealing with chemical safety.

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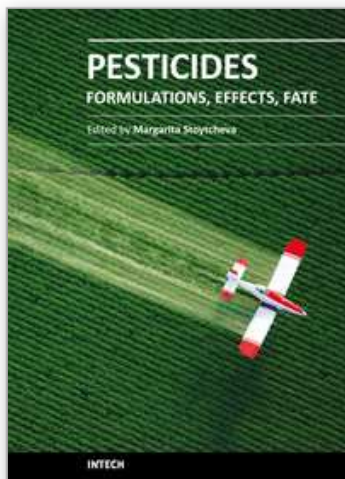
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Edited by Prof. Margarita Stoytcheva

ISBN 978-953-307-532-7

Hard cover, 808 pages

**Publisher** InTech

**Published online** 21, January, 2011

**Published in print edition** January, 2011

This book provides an overview on a large variety of pesticide-related topics, organized in three sections. The first part is dedicated to the "safer" pesticides derived from natural materials, the design and the optimization of pesticides formulations, and the techniques for pesticides application. The second part is intended to demonstrate the agricultural products, environmental and biota pesticides contamination and the impacts of the pesticides presence on the ecosystems. The third part presents current investigations of the naturally occurring pesticides degradation phenomena, the environmental effects of the break down products, and different approaches to pesticides residues treatment. Written by leading experts in their respective areas, the book is highly recommended to the professionals, interested in pesticides issues.

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Stavros Sifakis, Mihalīs Mparmpas, Offie P. Soldin and Aristides Tsatsakis (2011). Pesticide Exposure and Health Related Issues in Male and Female Reproductive System, Pesticides - Formulations, Effects, Fate, Prof. Margarita Stoytcheva (Ed.), ISBN: 978-953-307-532-7, InTech, Available from:  
<http://www.intechopen.com/books/pesticides-formulations-effects-fate/pesticide-exposure-and-health-related-issues-in-male-and-female-reproductive-system>

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