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Effect on Workers' Health Owing to Pesticides Exposure: Endocrine Target

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1. Introduction

Pesticides are used in agriculture and public health to control insects, weeds, animals, and vectors of disease. The Food and Agriculture Organization of the United Nations (FAO) defined a pesticide as '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 or otherwise interfering with the production, processing, storage, transport, or marketing of food, agricultural commodities, wood, wood products or animal feedstuffs, or which may be administered to animals for the control of insects, mites/spider mites or other pests in or on their bodies' (Bretveld et al., 2006).

Occupationally exposure to pesticides can occur in industry (manufacturing or formulation workers), agriculture (distribution on open fields or in closed premises, from crops), and in public health (disinfection, rodent elimination, etc.). Then, of course, some active principles are used in veterinary medicine.

In particular, for agricultural workers, we must remember that the work environment is often also the worker's home environment, since agricultural work is often done on a family or craftsman scale.

How workers are exposed may vary widely from one sector to another. An agricultural worker is likely to be exposed to numerous chemicals for short periods, and the level of exposure may vary depending on the type of crop involved, the climate or microclimate, what work is being done, the means used for distributing the chemical, and so forth.

Agricultural work in closed premises such as glasshouses or industrial plant-growing tunnels, and the formulation of commercial products (mixing the active principles with co-formulants) fall mid-way between agricultural and industrial work. Greenhouse work is done under cover with a constantly controlled microclimate, whereas industrial workers come into contact with various different products in different formulation cycles.

The integration of women into non traditional occupations raises questions concerning the impact of such jobs on women' reproductive health, moreover the number of women in the workforce is also increasing worldwide and a considerable proportion of them are of reproductive age; therefore attention is required to note reproductive dysfunction if any, due to occupational exposure (Kumar, 2004).

In literature occupational exposure to pesticides mainly could have repercussions on the reproductive system, in men and women, and on the thyroid gland. The epidemiological studies presented refer to the association between exposure in occupation of parents and the

incidence of infertility, congenital malformations, miscarriage, low birth weight, small-for-gestational-age (SGA) birth, preterm delivery and stillbirth.

The male reproductive system is vulnerable to the effects of this type of chemicals, this might be because sensitive events take place during spermatogenesis and some chemicals may affect some of these events to some extent.

The female reproductive system is also vulnerable but such data are fewer than male reproductive impairment data; this may be because male reproductive endpoints can be studied easier than the female, so that it is not easy to pinpoint which sex is more or less vulnerable to occupation related exposure. Some pesticides may interfere with the female hormonal function, which may lead to negative effects on the reproductive system through disruption of the hormonal balance necessary for proper functioning. Previous studies primarily focused on interference with the estrogen and/or androgen receptor, but the hormonal function may be disrupted in many more ways through pesticide exposure. Ovulation problems present themselves as irregular or absent menstrual periods and can be substantiated through measurement of reproductive hormones. Substances with estrogenic properties may be able to block ovulation similar to contraceptive pills.

An important question is whether occupational exposure of a parent can affect the offspring, causing malformations or reproductive system defects. There have, for instance, been reports of an increase in the risk of testicular dysgenesis syndrome, hypospadias and cryptorchidism, in the children of parents occupationally exposed to some substances (Vrijheid et al., 2003).

Beyond to the effects related to androgen and estrogen homeostasis, there is increasing evidence from animal and in vitro studies that also thyroid is vulnerable to some pesticides; the literature on thyroid-disrupting effects of individual chemicals is rapidly increasing, for some persistent compounds (Nicole-Mir, 2010); and the available evidence is much stronger and they may cause cognitive damage in humans, this effect may be mediated by induction of hypothyroidism, for other compounds is urgent to clarify their possible mechanism of interaction on this gland (Boas et al., 2006). We draw a general picture of pesticides with documented ability to interfere with the endocrine system and the impact achieved on health, with a look at prevention and protection of workers.

2. Pesticides in workplaces

As said workplaces involved in pesticides presence can be divided as agricultural and industrial one.

During occupational exposure these products are mainly absorbed by inhalation or through the skin. Absorption from the gastrointestinal tract is usually limited and is due to swallowing particles, because their size means they tend to deposit in the upper airways. On the topic of occupational exposure to these chemicals in agricultural work there is substantial agreement that the amounts inhaled – in the form of spray or vapors – are much less important than the part absorbed through the skin, except for fumigating agents which are extremely volatile. Contamination of the hands or other skin areas not covered or not otherwise properly protected by garments can account for a large proportion of what is absorbed – even exceeding half the total dose.

The risk of skin exposure to plant treatment products and pesticides has long been studied (Brouwer et al., 1992; Brouwer et al., 1992a; Muddy et al., 1990). In particular there has been close focus on the possible residual risk of handling hothouse plants and

flowers, and taking cuttings of plants that have been chemically treated is one situation that can pose problems: the risk depends largely on the volume of chemical applied and its specific characteristics, particularly its ability to penetrate the skin (Brouwer et al., 1992b; Simonelli et al., 2007).

2.1 Agriculture

The use of pesticides puts agricultural workers at particular “chemical risk”. They may come into contact with various preparations at different stages of their work and in every step is needed particular attention as precaution:

- When the pesticide is purchased. Before buying supplies it is essential to establish exactly how much is needed for immediate use, so as to avoid prolonged storage, with its risk of dangerous deterioration of the product.
- Transport of the pesticide is a delicate step, which calls for special precautions; suitable vehicles must be used, and the cargo must be safely loaded and firmly fixed in place. Pesticide containers should not be placed beside the driver.
- Storage of the product. The purchaser of a pesticide is responsible for all facets of its storage and use. It should be stored in premises only used for this purpose, and kept under key. These premises should not be underground or in semi-basements, and should be dry, well-ventilated and protected from frost.
- Preparation of the mixture. All pesticides, whatever their toxicological class, must be handled with special care. Always follow the directions on the label, using the recommended doses. Mixtures should be prepared outdoors, in a position sheltered from the wind.
- Loading the mixture into the spreader machinery. Spreading or distributing: all machinery should be inspected thoroughly before use with pesticides. Is important only use the products at the doses indicated on the label, following the manufacturer's instructions. Pesticides should be used by trained personnel, with the necessary qualifications or permits, wearing appropriate protective gear. The worker does not spread pesticides if people or animals are close by, or near houses. The direction and strength of the jets should be carefully adjusted so as to avoid dispersion of the product.
- Agricultural work in the treated areas.
- Maintenance work is essential to ensure the machinery is in good working condition, so as to avoid wasteful dispersion of the pesticide. This work must be done with the utmost care and attention, by personnel wearing the necessary individual protective apparel.

The risk is greatest when handling the concentrated product: opening the packs, weighing, mixing and loading into spreaders. Various factors can influence the risk of exposure; these include the weather (temperature, wind, humidity), and technical factors such as the method of distribution, individual protective gear, and the state of maintenance of machinery.

2.2 Pesticide manufacturing

Occupational exposure to pesticide is certainly a risk for workers who manufacture the active principles. In industrial processing the risk varies depending on the type of

formulation involved, meaning how the active principle is transformed for handling by the end user who normally dilutes it as directed for direct distribution on crops.
The following are some examples of formulations of plant protection products (table n. 1):

Dry powders dry formulations	The active principle is either pure or diluted in an inert powder (amorphous silicon, bentonite, colloidal clay, talc, wet colloids, etc.). These are used for dusting crops or land, foodstuffs or dry-tanning seeds.
Granulates dry formulations	The active principle is mixed in a granule of an inert substance. These are normally used as soil disinfectants or soil insecticides.
Soluble powders formulations for liquid treatments	The active principle is water-soluble. Mixed with water the powder dissolves, forming a solution in which it is uniformly, stably distributed. Some wettable powders are prepared in water-soluble packs.
Wettable powders formulations for liquid treatments	The active principle is solid, finely ground and not water-soluble. It can be suspended in water, but tends with time either to float or sink. This must be borne in mind when selecting the equipment to be used for distribution.
Emulsifiable concentrates formulations for liquid treatments	The active principle is dissolved in one or more organic solvents, giving an emulsifiable liquid that is not water-soluble. The drops remain suspended in the fluid used to distribute the product. Surfactants may be added to stabilize the formulation.
Water-based emulsions formulations for liquid treatments	The active principle is emulsified in water with specific coadjuvants to form an emulsion that remains stable for long periods (years).
Emulsifiable formulations for liquid treatments	These are stable suspensions containing fine particles of the active substance dispersed in an aqueous vehicle, with specific coadjuvants to form an emulsion that remains stable. Under this heading come formulations such as fluid and liquid pastes, concentrated suspensions, and colloid paste.
Suspension in microcapsules formulations for liquid treatments	The active principle is contained in tiny microspheres, dispersed in water with no solvents. The formulation is highly stable and the active substance is released gradually. This ensures greater, more lasting effect with less acute toxicity and phytotoxicity.
Dispersible and soluble granules formulations for liquid treatments	The active principle is finely ground with dispersing and wetting agents and prepared in microgranules that disperse or dissolve in water. They have the advantage of not creating dust and not leaving residues in the container.
Formulations for fumigation	Commercial formulations may be solid, liquid or gas. The active principles act in the gaseous form or as vapors. They are mostly used in closed premises, as insecticides or disinfectants for stocked foodstuffs, in soil or greenhouses.

Table 1. Some examples of formulations of plant protection products

The most dangerous step in the production of solid products is packing them, when workers may inhale the compounds as airborne dusts. The raw materials should ideally be mixed in closed systems. If open hoppers are used they should have hoods directly over them, connected to an aspiration system. The worker loading the product has to cut the bag and empty it, disposing of it in a container under an aspiration hood, to keep dispersion of dusts to the minimum. Hoppers loaded from big bags on special bag-emptying stands must also have their own aspiration hoods.

The use of the dangerous organochloride compounds is now forbidden in industrial processes and in agriculture, although they may arise in some settings as reaction intermediates. One example is in the production of chlorophenoxy herbicide (2,4,5 trichlorophenoxyacetic acid, sometimes called "Agent Orange") or intermediates in the synthesis of disinfectants (hexachlorophene). These processes require high pressure and temperatures, and an alkaline environment, and in these conditions dioxin, or TCDD, can easily form. In addition the reaction solvent is ethylene glycol, which can form unstable polymers that break down in a strongly exothermic reaction, raising the reactor temperature and pressure uncontrollably, with the synthesis of substantial amounts of dioxin, occasionally even blowing the safety valves (Schecter et al., 2006).

Both organic and inorganic mercury is used in the production of fungicides and this metal is well known to be neurotoxic and endocrine disrupter (Tan et al., 2009); cadmium is a frequent impurity in many phosphorus-based fertilizers and its presence could produce much more effects on endocrine system owing to its own ability to interfere as xenoestrogen (Chedrese et al., 2006; Takiguchi & Yoshihara, 2006).

3. Clinical-epidemiologic studies on workers

The toxicity of pesticides differs between the various active ingredients depending on numerous factors, first of all the lipid solubility, the acute pesticide poisonings are a frequent occurrence in developing countries while they are relatively infrequent in technologically advanced countries. In general, acute poisoning has resulted from accident or lack of or improper use of protective equipment, especially for substances with high dermal toxicity, (organochlorine and organophosphorus). Various devices and systems may be involved:

- Nervous system: neurotoxic effects are prominent in many pictures of poisoning by pesticides, they may be at central or peripheral level, they are manifested in the respiratory (chest tightness, coughing, cyanosis) , the gastrointestinal (nausea , vomiting, abdominal pain) or the cardiovascular system (hypotension, bradycardia). In particular, this kind of poisoning is due to organophosphorus insecticides, carbamates and organochlorines.
- Respiratory system: it is the target organ of intoxication caused by compounds belonging to the family of dipyridilic pesticides and urea derivatives, the most toxic compound in this picture is paraquat, poisoning can cause acute severe lung disease. The symptoms of this kind of intoxication consist of burning and irritation of the throat, with the presence of necrotic and scaling in the oral mucosa, after can occur gastroenteritis, wheezing, and cyanosis. The copper sulphate used as fungicide in viticulture and fruit production can cause lung injury described as "vineyard sprayers' lung" which consist of a micronodular interstitial pulmonary fibrosis. Less

important effects may also be caused by organophosphorus and carbamate insecticides.

- Coagulation: a family of rodenticides, the coumarins, are vitamin K antagonists and exert their toxic effect on coagulation, clinical sees bruising, epistaxis, hematuria, and in severe cases internal bleeding.
- Skin: from the clinical point of view are highlighted irritant or allergic contact dermatitis with manifestations of erythema, vesicles and scaling, the substances that most commonly produce these outcomes are the dithiocarbamates thiophthalimide and organochlorine insecticides.
- Liver and kidneys: for their anatomical structure and function there are bodies particularly susceptible to the action of toxic and therefore also of pesticides.
- Reproductive system: experimental studies suggest for a lot of compounds the ability to interact with the endocrine system and reproductive capacity.
- Carcinogenic and teratogenic effects: possible carcinogenic effects were seen for some phenoxy acid substances such as herbicides, chlorophenols, arsenical compounds, triazine herbicides.

There are many reports that a high proportion of pesticides interacts with the endocrine system – and the reproductive system in particular – through various mechanisms. In an Iranian study about 50% of the products used in agriculture could potentially interfere with the endocrine system, 33% of them leading to male infertility, 8% having estrogenic activity, 4.5% antiandrogenic, and 22% thyreostatic (Ebrahimi & Shamabadi, 2007).

Herbicides, insecticides and fungicides are the main endocrine disruptor chemicals (EDCs) likely to be encountered (carbofuran, chlopyrifos, dimethoate, lindane, trillate, triflurarin2,4-D and pentachlorophenol, linuron) (Eertmans et al., 2003).

Generally the toxic action does not involve a single mechanism, and several can be needed to cause pathology. Numerous *in vivo* and *in vitro* studies documented the receptor interactions of different compounds, but transposing these findings to humans is complex and still debated. The mechanisms of action can be grouped under several broad headings,

- Direct damage to cell structures
- Interference with biochemical processes necessary for normal cell function
- Biotransformation to toxic metabolites.

This is illustrated schematically in Fig. 1.

The dose, time and duration are all important pointers to the extent of exposure, as they all influence the real absorption of the toxin, hence its potential for harm (Bretveld et al., 2006).

3.1 Effects on reproductive system and on fetus

Some pesticides may interfere with the female hormonal function, which may lead to negative effects on the reproductive system through disruption of the hormonal balance necessary for proper functioning. Previous studies primarily focused on interference with the estrogen and/or androgen receptor, but the hormonal function may be disrupted in many more ways through pesticide exposure.

Studies in women have found menstrual cycle disturbances, with significant correlations between serum levels of 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) and its metabolites and polymenorrhea (missing several cycles) (Windham, 2002). A survey of 3103 women agricultural workers found that those handling and distributing pesticides – usually

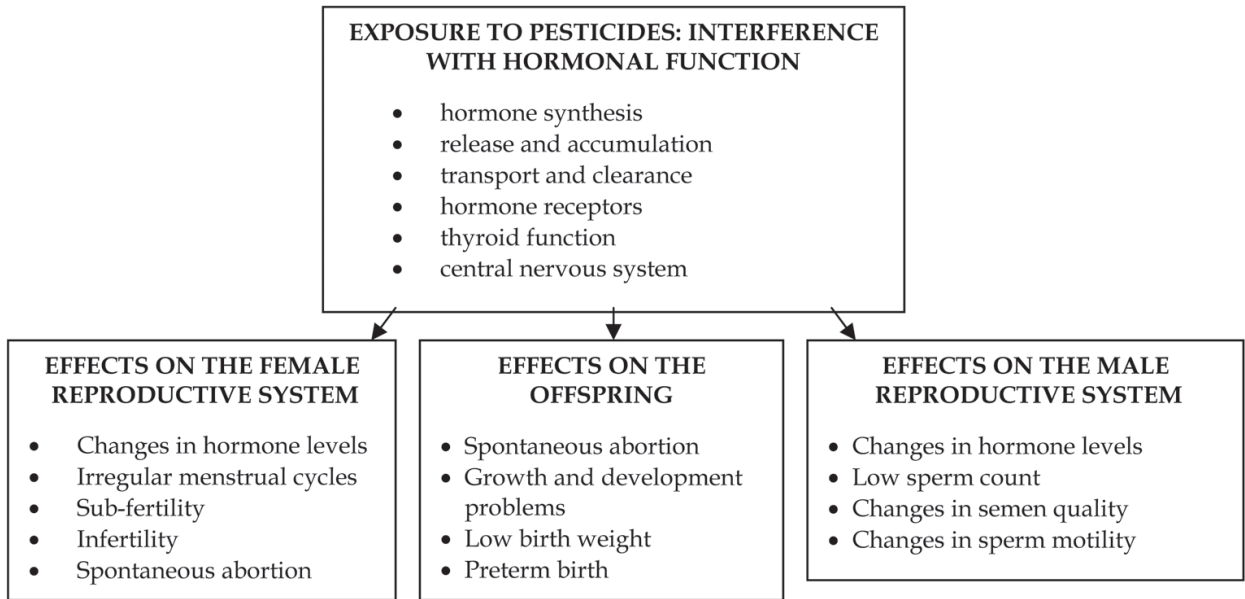


Fig. 1. Mechanisms of action of pesticides on endocrine system

mixtures – had 60-100% more episodes of amenorrhea (no menstruation) (Farr et al., 2004). Both found associations between serum levels of DDT or a metabolite of DDT and short cycles and undefined 'menstrual disturbances'. Another study found no correlations between infertility and self-reported overall pesticide exposure, working in the agricultural sector, or living on a farm during the two years before the diagnosis of infertility or the last pregnancy. The pesticides may disrupt the hormonal function of the female reproductive system and in particular the ovarian cycle (Bretveld et al., 2006).

Pesticide use may be associated with a later age at menopause.

Few other studies have examined the association between specific pesticide exposure and timing of natural menopause reported an increased hazard ratio (earlier age at menopause) for women with higher plasma levels of p,p'-1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (an isomer of DDE), a breakdown product of the pesticide DDT, using data from 1,407 women in a breast cancer case-control study. Furthermore these type of research are controversial and the results were not clear. This difference may be due to different sampling or exposure assessment strategies. The toxicology evidence, along with the two existing epidemiologic studies examining DDE and timing of menopause, it's hypothesized that use of hormonally active or ovotoxic pesticides would result in an earlier menopause in women by depleting germ cells in the ovary. However, there was no evidence in some analyses that use of pesticides led to an earlier menopause. On the contrary, taken together, use of hormonally active pesticides was associated with later age at menopause. Later age at menopause is associated with fertility in later reproductive years and possibly with an increased risk of certain reproductive cancers but a decreased risk of cardiovascular disease and overall mortality (Dalvie et al., 2004a).

A recent study reported a reduction in age-adjusted all-cause mortality by 2 percent per year increase in age at menopause. Use of pesticides was associated with a delay of 3–5 months in timing of menopause. Number of ovulatory cycles has been inversely associated with age at menopause, while cycle length has been positively associated with age at menopause. Additional analyses among younger women in the Agricultural Health Study showed that exposure to hormonally active pesticides was associated with longer menstrual cycles and

more missed menstrual periods. Pesticide exposure may lead to a later age at menopause through effects on menstrual cycles. Alternatively, hormonally active pesticides may directly affect timing of menopause through effects on follicle-stimulating hormone and luteinizing hormone. Women who use pesticides may be healthier overall than women who do not use pesticides. Among 8038 workers recruited, 62% had handled and applied various pesticide mixtures (DDT, lindane, atrazine, carbaryl, carbon tetrachloride, mancozeb and maneb, organochloride compounds, carbamates, organophosphorus compounds, phenoxy herbicides); these workers all reported a lengthening of the time of onset of the menopause, of about three to five months (Farr et al., 2006).

A Danish study of women distributing pesticides in greenhouses found a clear reduction in fertility (reduced fecundity pregnancies per month while trying to get pregnant) (Abell et al., 2000); this was also seen in Finnish workers (Taskinen et al., 1995; Sallmen et al., 2003). In the USA the incidence of lowered fertility was three times higher in women exposed to pesticides than among other women agriculture workers, and as much as nine times higher than non-agricultural workers (Fuortes et al., 1997; Smith et al., 1997). However, some of these findings have been questioned even though exposure to herbicides seems the most significant factor (Greenlee et al., 2003).

Several studies have set out to assess the effects on reproductive health by recording any abnormalities during pregnancy: spontaneous abortion, stillbirths, fetal malformations, preterm births, low birth weight. The data are not always clear or easily correlated to the real exposure conditions, for instance to DDT (Cocco et al., 2005; Dalvie et al., 2004a): in vivo and in vitro toxicological findings may be evident but epidemiological studies have not given univocal results, often because the sample had poor statistical strength or the methods were not altogether correct. Some studies found a significantly higher risk of spontaneous abortion among women directly exposed to pesticides (Arbuckle et al., 1999; Arcuckle et al., 2001; Nurminen, 1995; Petrelli et al., 2000a; Crisostomo & Molina, 2002) although it was not clear through what mechanism of interaction with the endocrine system this effect was achieved (Hanke & Jurewics, 2004). A study of exposure to phenoxy herbicides in 2000 couples found only weak correlations between spontaneous abortion and exposure up to three months before conception; however, the correlation became stronger, up to double the risk of controls, for exposure in the weeks immediately preceding conception (Arbuckle et al., 1999), the outdoor agricultural workers showed much less data (Degen & Bolt, 2000).

The data on the effect of employment in agriculture on the time to pregnancy are unequivocal, but most of them suggest that there is a relationship between the decreased fecundability ratio and pesticide exposure. Nor does the research on the sex ratio of offspring provide explicit results. The analyses indicate that parental employment in agriculture could increase the risk of congenital malformations in the offsprings, particularly such as orofacial cleft, birthmarks in the form of hemangioma as well as musculoskeletal and nervous system defects. The data on the effect of occupational exposure to pesticides on birth weight are contrasting. Although most of epidemiological studies do not reveal a significantly increased risk of SGA, a slower pace of fetal development corresponding to SGA in the population of women exposed to pyrethroids has been recently reported. There are also some indications that exposure to pesticides may contribute to stillbirth and female infertility. There are a Danish follow-up studies to examine whether exposure to pesticides during pregnancy had an adverse effect on pregnancy outcomes among gardeners and farmers. There were no significant differences in the studied pregnancy outcomes between gardeners or farmers and all other workers, except for an increased risk of very preterm birth for gardeners and a favorable birth weight for farmers (Zhu et al., 2006).

A study investigated whether the work in greenhouse during pregnancy adversely influenced infant birth weight. Work in greenhouses is performed in warm microclimate during the most time of the year, involves usually moderately intense or heavy work. The working conditions in greenhouses might involve also indirect exposure to pesticides resulting from contact with pesticide-treated flowers and vegetables. Results indicate that infants of mothers performing heavy work inside greenhouse during pregnancy had lower mean birth weight than infants of mothers working out of greenhouse. No similar effects of current exposure to pesticides was observed (Jurewicz et al., 2005).

A study of the effects of thiocarbamates and carbaryl in 3984 pregnant women in Canada found a higher risk of spontaneous abortion; the increase in risk was less evident for pre-gestational exposure to phenoxy acetic acid and triazine herbicides, and late spontaneous abortion was associated with the use of fungicides, thiocarbamates and glyphosate (Arbuckle et al., 2001). Most of these miscarriages happened in the first trimester of pregnancy. A North American study correlated the occupational use of herbicides (sulphonylurea, imidazolinone and mixtures of chlorophenoxy herbicides, sulphonylurea and benzothiodazole) with an increase in spontaneous abortions in spring, and results were similar for Ethylen-bis-dithiocarbamates fungicides, particularly maneb and mancozeb. The period of exposure to pesticides is important, as different climatic conditions may influence the level of exposure and the potential effects. There is a surprisingly significant deficit in the number of male children born to the spouses of fungicide applicators. First-trimester miscarriages occur most frequently in the spring, during the time when herbicides are applied. Use of sulphonylurea, imidazolinone containing herbicides, and the herbicide combination by Cheyenne male applicators was statistically associated with increased miscarriage risk in the spring. Limited survey data from women who are the spouses of applicators did not show major alterations of long-term endocrinologic status (menarche, menopause, endometriosis) (Garry et al., 2002).

Various studies report malformations in the neonates (limb anomalies, cleft lip/palate) (Hanke & Jurewics, 2004) but subsequent epidemiological surveys did not always confirm this (Clementi et al., 2007). An excess risk of musculoskeletal malformations was reported among children born to Finnish garden-workers (Hemminki et al., 1980) and a higher than normal risk of angioma was noted for the infants of flower-growers in a population of 8867 workers from Bogota (Restrepo et al., 1990). A Spanish study correlated exposure to pyridyl derivatives with risks for the nervous system, cleft lip/palate and multiple anomalies (Garcia et al., 1998) but no increase in risk for exposure to organophosphorus compounds, carbamates, organochlorides, fungicides and organosulphates (Garcia et al., 1999). An increased risk of cleft lip/palate was found also in Finland (Nurminen et al., 1994) and of spina bifida and hydrocephalus, particularly among mothers exposed in orchards and greenhouses, in Norway (Kristensen et al., 1997a).

A rise in fetal malformations therefore seems to be associated, more or less decisively, with handling chlorophenoxy herbicides (Schreinemachers, 2003), fungicides, trifluralin, atrazine (Garry et al., 1996), and phosphine and glyphosate-based products used for fumigation (Engel et al., 2000).

Data on low birth weight of babies born to women exposed to pesticides are also discordant. In Canada (Robert, 1988), Scotland (Saniose et al., 1991) and Norway (Kristensen et al., 1997a) the figures were the same as for controls, whereas in Indonesia (Murphy et al., 2000), Brazil (Lima et al., 1999) and Poland (Dabrowski et al., 2003; Hanke et al., 2003) birth weight was about 100 g lower than normal for women exposed in the first trimester of pregnancy, particularly to pyrethroids (Hanke et al., 2003).

Attempts to clarify the correlation between pesticide exposure and stillbirths have also found a confused picture (Bell et al., 2001). Californian studies indicated that exposure in the second trimester of pregnancy, particularly the third and fourth months, to carbamates and acetylcholinesterase inhibitors could increase the risk of stillbirth (Goulet & Theriault, 1991), but Kristensen et al. in Norway found no significant effects (Kristensen et al. 1997a; Kristensen et al. 1997b).

Organophosphorus pesticides raise a different question, as their acetylcholinesterase inhibition is associated with the possibility of interaction with hypothalamic and/or pituitary function, hence gonadal processes. Hormone assays have been used as a means of documenting these effects. A study from Pakistan (Ahmad et al., 2004) that measured acetylcholinesterase activity in women occupationally exposed to organophosphorus compounds found that half the workers had only 34.42% of the controls' activity; about 40% had 72.59% of the activity and 8% had 87.94%; the percentage of "toxicity" calculated in relation to age came to 18.42%. Excluding seven cases of acute intoxication, one third of the women reported oligomenorrhea, another third secondary amenorrhea, 16.67% early menopause and 16.67% heavy menstrual flow; there were no cases of infertility.

Serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone levels, as well as urinary levels of FSH, LH, and E1C, a metabolite of testosterone, were measured to investigate the adverse reproductive effects of organophosphate pesticides among Chinese factory workers who were occupationally exposed to ethylparathion and methamidophos. The exposure significantly increased the serum LH. Meanwhile, the serum FSH level was slightly elevated and the serum testosterone level was decreased with increased pesticide exposure. It's possible conclude that organophosphate pesticides have a small effect on male reproductive hormones, suggestive of a secondary hormonal disturbance after testicular damage (Padungtod et al., 1998).

This was confirmed by Recio et al. (Recio et al., 2005) who found that out of 64 agricultural workers 48% had FSH outside the normal range, with values substantially higher than normal during the periods of highest pesticide use; LH was also slightly elevated, but no abnormal findings were recorded for testosterone.

Exposure to organophosphorus pesticides has been associated with changes in the chromatin structure of sperm, which may raise the proportion of cells highly susceptible to DNA denaturation (Sanchez-Pena et al., 2004); these compounds also interfere with spermatogenic chromosomal segregation, again raising the risk of genetic damage (such as Turner's syndrome) because of aneuploidy (Recio et al., 2001).

Significant associations have been found between serum levels of organochlorides and immune and endocrine alterations, indicative of the risk that these products interfere in the course of gestation (Gerhard et al., 1998). In 20% of women agricultural workers with repeated spontaneous abortion, serum assays found at least one polychlorinated hydrocarbon outside the reference range (Eckrich & Gerhard, 1992), and high levels of DDT and DDE in maternal blood were also associated with preterm birth and the infant's size and weight (Gerhard et al., 1999b). Another study, in women exposed to pentachlorophenol – used to protect wood – suggested a central interaction for this product, which might act in the hypothalamus or at suprahypothalamic levels, leading to ovarian and adrenal insufficiency (Gerhard et al., 1999a).

Epidemiologic studies of the negative effects on the male reproductive system have looked at semen and sex hormones when the aim was to investigate male fertility directly (Hess & Nakai, 2000; Giwercman et al., 1993; Silvestroni & Palleschi, 1999; Larsen et al., 1999) or

“man-mediated” effects, i.e. generally time to conception (Petrelli et al., 1999; De Cock et al., 1994; Curtis et al., 1999). Neither approach found univocal data, and more specific investigations are needed to see which particular type of chemical is involved and in what conditions of exposure (Petrelli & Mantovani, 2002). Experimental investigations on semen often found no real differences in morphology (Smith et al., 2004) particularly the effects of exposure to fungicides, have also not proved significant this exposure does not cause aneuploidy of the spermatozoa, unlike smoking which is a strong confounding factor (Smith et al., 2004; Harkonen et al., 1999) or sperm count (Golec et al., 2003). This illustrates the difficulties of establishing clear correlations between these biological data and potential reductions in fertility, which tend to be suggested more by studies based on “time to pregnancy” (Hanke & Jurewics, 2004; Petrelli et al., 2000b; Bonde et al., 1999).

The most significant findings come from epidemiologic studies focused on handling the most toxic products, whose biological effects are documented better, like DDT, which is still used in many developing countries to get rid of the mosquitoes that cause malaria, in fact in a study of workers using DDT to control the carriers of malaria found that clinically significant exposure was correlated with antiandrogen or estrogenic effects that might possibly cause abnormal levels of reproductive hormones, the most important finding was a positive relationship of baseline E2 and baseline testosterone with blood DDT compounds levels, especially with p'p'-DDT and -DDD. Peak post- GnRH testosterone was also positively related to p'p'-DDE. (Dalvie et al., 2004a). These studies found that 84% of workers handling these compounds had a sperm count below the levels indicated by the WHO and below Tygerberg's criterion, with 6% fulfilling Tygerberg's definition of subfertility; 10-20% complained of sexual dysfunction. Although DDT has little xenoestrogenic capacity - it is 103-106 times less potent than estradiol - its bioaccumulation may lead to estrogenic effects in certain circumstances, and at high doses it is an androgen agonist (Gray & Kelce, 1996; Toppari, 1996; Kelce, 1995).

Numerous pesticides directly harm the spermatozoon, altering the function of the Sertoli or Leydig cells, or interfering with endocrine function at various stages in hormonal regulation. These mechanisms have been amply documented *in vivo* and *in vitro* but are hard to record in epidemiologic terms (Bretveld et al. 2007) because of the specificity of occupational exposure, since the extent of exposure and its effects must be quantified exactly to clarify the negative effects on health.

More significant results come from studies aimed at detecting correlations between occupational exposure and abnormal hormone levels. In these cases even low-dose exposure can cause changes that are detectable in blood assays. Strambe et al. (Straube et al., 1999), for instance, found that acute exposure to herbicides, insecticides and fungicides in agricultural workers lowered the levels of testosterone and estradiol, while slightly raising T4 and T8 lymphocytes. Chronic exposure, on the other hand - which is closer to real working situations - led to higher testosterone levels and a higher T4:T8 ratio; in addition the LH concentration was higher than in controls. The authors concluded that the interaction involved inhibition of the aromatase system in the testosterone metabolism. Quite likely there is some interference with both the endocrine and immune systems, certainly depending on the exposure time.

Similar findings came from a study of 114 herbicide application workers who had high levels of testosterone, FSH and LH, and alterations to thyroid hormone levels too (Garry et al., 2003): in the herbicide-only applicator, significant increases in testosterone levels in fall compared to summer and also elevated levels of follicle-stimulating hormone (FSH) and

luteinizing hormone (LH) in the fall were noted. Historic fungicide use was associated with a significant alteration of the sex ratio of children borne to applicators. Lower testosterone level were associated with a shift in the sex ratio of children born to applicators. As before, among current study subjects it was noted that historic fungicide use was associated with increased numbers of girls being born.

Brazilian epidemiologic survey detected significant correlations between mortality from hormone-related tumors (ovary, prostate, testes) and at least ten years of intensive agricultural work (Koifman & Koifman, 2002).

Male reproductive toxicity involves a broad range of targets and mechanisms such as direct effects on the seminiferous epithelium and/or on Leydig and Sertoli cells supporting spermatogenesis, epididymal sperm maturation as well as endocrine disruption. Male subfertility is generally expressed as a reduced ability of the female partner to become pregnant. Male workers exposed to some pesticides have shown a decreasing number of spermatozoa and alteration of semen quality and morphology. Moreover prenatal exposure could induce testicular dysgenesis syndrome, hypospadias and cryptorchidism. (Carbone et al., 2006; Pierik et al., 2004). A father's exposure to pesticides at work predicted an adverse live-birth outcome (preterm delivery) in multivariate models (Hourani & Hilton, 2000).

Other authors find no real differences in semen quality (Larsen et al., 1999) and no correlation between exposure and reduced fertility (time to pregnancy) (Thonneau et al., 1999). Workers most likely to be exposed, besides agricultural laborers who prepare the pesticide mixtures, are those who work land or crops that have been treated, and the pilots of planes used to spray these products. Evaluation of the negative effects on greenhouse workers exposed to pesticides showed that their wives tended to have a long time to pregnancy (Petrelli et al., 2000b).

3.2 Thyroid and hormonally dependent cancers

Carcinogenesis (cancer formation) involves irreversible alteration of a stem cell, its uncontrolled proliferation and, finally, invasion of other tissues. In this sequence there are various mechanisms by which pesticides may contribute to cancer development. The most obvious mechanism is genotoxicity, direct alteration of DNA turning harmless cells into cancer cells. Even levels of exposure to organophosphates too low to significantly decrease cholinesterase levels increased chromosomal aberrations found in blood samples from farmers. Pesticides thought to cause cancer in this way include the fumigants ethylene oxide and ethylene dibromide.

Pesticides and other endocrine disrupters represent a credible "new" risk factor for hormonally dependent cancers. To date, most work has centered on breast cancer, and most studies have not shown increased risks. Additional epidemiologic investigations are warranted, but they would benefit from a better understanding of the mechanisms, dose, and co-factors involved (Muir, 2005).

An American study showed that, among women farmers, breast cancer risks were elevated for women present in fields during or shortly after pesticide application, but not among those who reported using protective clothing. Some data showed a weak association between breast cancer and farming. DDT can support the growth of estrogen-dependent tumors in rats. However, most case-control studies since 1996 have failed to confirm earlier observations of a significant positive relationship between levels of DDT and DDE (a DDT breakdown product) to breast cancer risk.

	REPRODUCTIVE TOXICITY	REFERENCES
1,1,1-TRICHLORO-2,2-BIS(P-CLOROPHENYL)ETHANE (DDT)		
Female reproductive system	Menstrual cycle disturbances, polymenorrhea, block ovulation, irregular or absent menstrual periods.	Windham, 2002 Bretveld et al., 2006
	Increases in spontaneous abortions	Arbuckle et al., 1999 Petrelli et al., 2000a Nurminen, 1995 Crisostomo & Molina, 2002
	Preterm births and low birth weight	Gerhard et al., 1999
Male reproductive system	Alterate secretion of testosterone	Dalvie et al., 2004a
	Low sperm count, subfertility, sexual dysfunction	Dalvie et al., 2004b Gray & Kelce, 1996 Toppari, 1996 Kelce, 1995
CARBAMATES		
Female reproductive system	Increases in oligomenorrhea	Farr et al., 2004
	Increases in spontaneous abortions	Arbuckle et al., 2001
	Risk of stillbirth	Goulet & Theriault, 1991
HERBICIDES		
Female reproductive system	Amenorrhea	Farr et al., 2004
	Increases in spontaneous abortions	Arbuckle et al., 1999 Garry et al., 2002 Taskinen, 1992
	Increased miscarriage risk	Garry et al., 2002
	Longer time to pregnancy	Petrelli et al., 2000b
Male reproductive system	Alterations in sex hormone output	Staube et al., 1999; Garry et al., 2003
FUMIGANTS		
Female reproductive system	Polymenorrhea	Farr et al., 2004
MIXTURES (DDT, lindane, atrazine, carbaryl, carbon tetrachloride, mancozeb, maneb, carbamates, organophosphorus compounds, phenoxy herbicides)		
Female reproductive system	Prolongation of time to menopause	Farr et al., 2004
	Reduced fertility	Abell et al., 2000 Taskinen et al., 1995 Sallmen et al., 2003 Fuortes et al., 1997 Smith et al., 1997 Greenlee et al., 2003
Male reproductive system	Alterations in sex hormone output	Staube et al., 1999; Garry et al., 2003
FUNGICIDES		
Female reproductive system	Increases in spontaneous abortions	Arbuckle et al., 2001 Garry et al., 2002
Male reproductive system	Alterations in sex hormone output	Staube et al., 1999;

		Garry et al., 2003
ORGANOPHOSPHORUS COMPOUNDS		
Female reproductive system	Oligomenorrhea, secondary amenorrhea, early menopause, heavy menstrual flow	Ahmad et al., 2004
	Alterations in sex hormone output	Padungtod et al., 1998 Recio et al., 2005
Male reproductive system	Reducing brain acetyl cholinesterase activity and monoamine levels, thus impairing hypothalamic and/or pituitary endocrine functions and gonadal process	Recio et al., 2005 Garry et al., 2003
	Decreased testosterone levels, testicular damage, sperm hyperploidy/polyploidy	Padungtod et al., 1998 Recio et al., 2001
	Alterations to chromatin structure of sperm	Shanchez-Pena et al., 2004
	Aneuploidy of sperm	Recio et al., 2001
MIXTURES (Chlorophenoxy herbicides, fungicides, trifluralin, atrazine, phosphine and glyposate-based fumigants)		
Neonatal/fetal malformations from parental exposure	Anomalies of the limbs, cleft lip/palate	Hanke & Jurewics, 2004 Nurminen et al., 1994
	Musculoskeletal malformations	Hemminki et al., 1980
	Risk of angioma	Restrepo et al., 1990
	Multiple anomalies	Garcia et al., 1998
	Spina bifida, hydrocephalus	Kristensen et al., 1997
MIXTURES (ethylparathion and methamidophos)		
Female reproductive system	Increased serum LH and FSH, decreased testosterone levels	Padungtod et al., 1998 Garry et al., 2003
MIXTURES (pesticides)		
Female reproductive system	Later age at menopause	Farr et al., 2006
Male reproductive system	Decreased number of spermatozoa, alteration of semen quality and morphology, aneuploidy of spermatozoa	Carbone et al., 2006 Pierik et al., 2004 Harkonen et al., 1999
Neonatal/fetal malformations from parental exposure	Low birth weight, small-for-gestional-age (SGA) birth, testicular dysgeneris syndrome, hypospadia and cryptorchidism	Hanke & Jurewicz., 2004 Hourani & Hilton, 2000 Jurewicz et al., 2005 Abell et al., 2000

Table 2. Summary of relation between pesticides and effects on human reproductive system

The use of Chlordane, malathion, and 2,4-D was associated with increased risk of breast cancer; risk associated with chemical use was stronger in younger women (Mills & Yang, 2005).

There is some evidence linking pesticide exposure and ovarian cancer, but findings are inconsistent. Italian research showed an association between exposure to triazine herbicides and ovarian cancer (Donna et al., 1984)

Epidemiology studies have investigated the possibility that atrazine may result in adverse effects in humans. The chloro-S-triazine herbicides (i.e., atrazine, simazine, cyanazine) constitute the largest group of herbicides. Despite their extensive usage, relatively little is known about the possible human-health effects and mechanism(s) of action of these compounds. Studies in laboratory have shown that the chlorotriazines disrupt the hormonal control of ovarian cycles. Results from these studies hypothesized that these herbicides disrupt endocrine function primarily through their action on the central nervous system. Although some studies have claimed that atrazine exposure results in an elevated risk of prostate cancer, the published literature is inconclusive with respect to human cancer incidence. But studies of prostate cancer are beginning to show consistent associations with pesticide exposure.

Case-control in Sweden and in USA studies confirm that exposures to cadmium, herbicides, and fertilizers low occupational physical activity levels have elevated prostate cancer risks. Increased risk with specific chemicals, simazine, lindane, and heptachlor suggestive increases with dichlorvos and methyl bromide (Settimi et al., 2003; Settimi et al., 2001; Sharma-Wagner et al., 2000; Mills & Yang 2003; Gammon et al., 2005).

The study among rural workers in Brazil indicated an almost two times higher probability of cancer development among rural workers, with a calculated relative risk between those exposed (agriculture workers) and the non-exposed (other occupations) of 1.6. The authors concluded that the cancers of the skin and digestive system were the most prevalent.

There are numerous reports on the possible effects of exposure to pesticides on the thyroid, in fact thyroid gland diseases (goiter, autoimmune thyroiditis, carcinoma) are associated with exposure to many chemical or physical agents (Baccarelli, 1999). Among these substances fungicides are largely studied for their impact on thyroid, particularly ethylenebis (dithiocarbamates) (EBDCs), such as maneb, zineb and mancozeb, they have been extensively used for the past 40 years; EBDCs are metabolized into ethylenethiourea (ETU), a possible human carcinogen and an antithyroid compound, so that the Environmental Protection Agency (EPA) of the United States of America has restricted their use and require workers to use protective equipment. ETU is known to cause decreases of thyroxine (T4) and increases in thyroid-stimulating hormone (TSH) in animals, researches on working population suggest that EBDCs affect the thyroid gland among heavily exposed workers even if data are yet of borderline statistical significance (Steenland et al., 1997). This trend of thyroid hormones levels is confirmed in a study on banana plantation workers, correlated with blood and urinary ETU levels, moreover was founded a higher prevalence of solitary nodules in exposed workers as detected by ultrasound (Panganiban et al., 2004). Farmers who had aerial application of fungicides to their land showed a significant shift in TSH values; subclinical hypothyroidism was noted in rural applicators (TSH values >4.5 mU/L), but not in urban control subjects.

The level of TSH was elevated also in male pesticide formulators exposed to the dust and liquid formulation of endosulfan, quinalphos, chlorpyrifos, monocrotophos, lindane, parathion, phorate, and fenvalerate as compared to a control group, but the increase was statistically insignificant (Zaidi et al., 2000).

The serum levels of thyroxine and thyroid stimulating hormone were examined in rural subjects with respect to blood levels of organochlorine pesticide, it's found that some subjects had depleted thyroxine levels in association with significantly lower organochlorine pesticide residues in blood. Sex, nutritional status, thyromegaly, or handling of pesticides in the course of work were not found to be factors contributing to depleted thyroxine levels (Srivastava et al., 1995). All informations about effect on thyroid and cancer are reported in table n. 3.

	Type of exposure	Observed effects	References
Thyroid	Pesticides	Goiter, autoimmune thyroiditis	Baccarelli, 1999
	Endosulfan, quinalphos, chlorpyriphos, monocrotophos, lindane, parathion, phorate, and fenvalerate	Significant shift in TSH values; Subclinical hypothyroidism	Zaidi et al., 2000
	Hexachlorbenzene--HCB, DDE (2,2'-2-bis(4-chlorobiphenyl)- 1,1-dichloroethylene), p,p'-DDT (2,2'-bis(4-chlorophenyl)- 1,1,1-trichloroethane) and alpha-, beta- and gamma-hexachlorcyclohexane--HCH)	Increased thyroid volume higher frequency of hypoechogenicity and frequency of positive thyroperoxidase antibodies level in blood	Panganiban et al., 2004 Srivastava et al., 1995
	Organochlorine pesticide	Depleted thyroxine levels, thyromegaly, increased TSH	Steenland et al., 1997
Cancer effects ("new" risk factor for hormonally dependent cancers)	Chlordane, malathion, and 2,4-D; DDT and DDE	Breast cancer	Mills & Yang, 2005 Donna et al., 1984
	Atrazine herbicides, and fertilizers, simazine, lindane, and heptachlor	Prostate cancer	Setimi et al., 2003 Settimi et al., 2001 Sharma-Wagner et al., 2000 Mills & Yang, 2003 Gammon et al., 2005
	Organophosphorous pesticides	Tyroid cancer	Baccarelli, 1999

Table 3. Dysfunction on thyroid gland due to pesticides in farming and hormonally dependent cancers.

4. Difficulties in epidemiological studies

There is much debate about the best methodological approach for epidemiological studies of exposure to Endocrine disruptor chemicals. Assessment of exposure to endocrine disrupters is complicated because of wide variation in endocrine disrupting potency of

substances and mechanisms by which these compounds produce their effects, and because little is known about possible interactions that may occur in exposure in many occupations. Some authors have developed a job-exposure matrix for potential endocrine disrupting chemicals, seven categories of contaminants were evaluated, for trying to obtain a more simple approach to the problem, but the job-matrix does not distinguish substances with different mechanisms or potency for endocrine disruption, nor does it incorporate any possible changes in exposure over time, and all these conditions represent great limits to its use (van Tongeren et al., 2002).

A protocol for assessing the risk of occupational exposure has been proposed, giving broad outlines, starting with risk identification and continuing through to defining dose-response relationships (Taskinen & Ahlborg, 1996). Unfortunately there is still no agreement on the validity of these questionnaires for collecting the occupational history of workers exposed to PCB. The risk of incorrect data is estimated at 13-29% and a tendency has been noted to overestimate exposure for women; for men the distribution was random (Rosenberg et al., 1987).

To overcome this problem a standardized procedure has been proposed, based on the application of two statistical tests, Gibbons' Alternative Minimum Level (AML), and a test to establish the relative standard deviation (RSD); the aim is to achieve the necessary reproducibility for data concerning biological monitoring of workers exposed to PCB. The method was validated on data collected in 1960 and gave good precision, with a low limit of detection (Willman et al., 2001).

A pivotal question is the "measure" that accurately describes exposure. This is much more difficult than checking for reproductive problems and is present as much in case-control studies in workers as in the general population. To minimize gross error it is recommended to pool biological findings with information from questionnaires, taking great care to select accurate and reliable statistical methods, based primarily on metabolic considerations (What function does the biological mechanism alter?) (Joffe, 1992).

Interpreting the results and putting them to use to prevent harm to health is a focal point, but transposition is not easy. It is also no simple matter to establish environmental and biological "cut-offs" that will adequately safeguard endocrine health (Figà-Talamanca & Giordano, 2003).

On the subjects of reproductive health, a Scandinavian group of Danish, Norwegian and Finnish researchers has proposed a classification criterion for substances causing reproductive toxicity, this takes account of epidemiological and experimental toxicology findings, to give a versatile tool for planning and verifying preventive measures in the workplace (Taskinen, 1992).

Time to pregnancy is one of the most widely used indicators and the standardized birth ratio is another – this is the ratio of observed to expected births; failure to conceive after a year of unprotected sexual relations is considered true infertility.

Epidemiological studies on occupational exposure and fertility often suffer from bias (Castilla et al., 2001). Confounding factors are important in these investigations (some are listed in Table 4).

In view of the considerable difficulties of these studies, the World Health Organization has evaluated all the data regarding the impact of work on reproductive health and the final report states that only 10% of published epidemiological studies can be considered methodologically correct.

CONFOUNDING FACTORS	
MEN	WOMEN
Drugs, alcohol, smoking Anatomical abnormalities of the genital organs Cryptorchidism Parotitis Hormonal dysfunction Diabetes mellitus Varicocele Testicular trauma	Drugs, alcohol, smoking Ovarian dysfunction Hyperandrogenism Endometriosis Hormonal dysfunction Genital infections Uterine factors Factors involving the uterine cervix Causes originating from a fetus

Table 4. Confounding factors in Epidemiological studies

5. Conclusions and prospects

Research in recent years has investigated the toxic effects of many compounds on the reproductive system in men and women. This is an important area because of the infinite implications of any such alteration: from the possibility of conception, through a normal pregnancy, to the birth of a healthy child. Physical health is not the only factor involved, because the emotional sphere is brought into play too. This is illustrated by the major psychological problems raised by infertility, and the tortuous diagnostic-therapeutic paths couples are willing to follow to overcome it.

One very important factor is previous environmental exposure, which largely influences the “internal” dose in the general population, especially for lipophilic contaminants that accumulate in adipose tissue and persist at length. For instance, the general population has blood levels of PCB comparable to those resulting from low-dose exposure, which makes it very complicated to check for any dose-response correlation (Hanaoka et al., 2002).

Thyroid diseases are increasing in the general population , especially among women. Although the most frequent dysfunctions have either an auto-immune or congenital etiology, the possible effects of environmental factors on the normal homeostasys should not be overlooked. The identification of the single responsible substances is complex because of its multiple target action as well as the possible interference of the complex network involving thyroid hormones their metabolism and their functions. Pesticides influence the thyroid endocrine activity trough the inhibition of thyroid peroxidase (TPO) or trough alteration of the production of thyroid hormones (T3, T4), their transport, their secretion and biosynthesis activity of this gland, and sensorial alterations especially trough the genetic adjustment of the response to T3 (Schmutzler et al., 2004; Beard & Rawlings, 1999). Among these the most significant are ethil-bi-dithio carbamate as well as some persistent chlorurate compounds.

Occupational exposure is certainly an area calling for much further research (Hoyer, 2001; Crews et al., 2000) which might take several directions:

- identification of all the chemicals that can be toxic to the endocrine system;
- description and evaluation of exposure;
- definition of the dose-response paradigm, which is a tough task on account of the widespread environmental presence of contaminants;

- identification of environmental and biological concentrations above which there is a real health risk;
- development of validated analytical methods;
- agreement on reference intervals for biological assays;
- consensus on the exact definition of "low doses";
- drafting operational protocols for epidemiological studies for the workplace;
- assessment of personal susceptibility, especially as regards sex difference.

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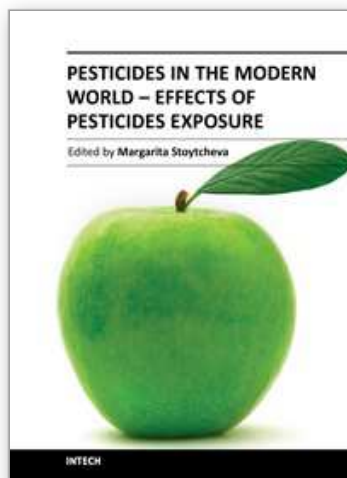
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Pesticides in the Modern World - Effects of Pesticides Exposure

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The introduction of the synthetic organochlorine, organophosphate, carbamate and pyrethroid pesticides by 1950s marked the beginning of the modern pesticides era and a new stage in the agriculture development. Evolved from the chemicals designed originally as warfare agents, the synthetic pesticides demonstrated a high effectiveness in preventing, destroying or controlling any pest. Therefore, their application in the agriculture practices made it possible enhancing crops and livestock's yields and obtaining higher-quality products, to satisfy the food demand of the continuously rising world's population. Nevertheless, the increase of the pesticide use estimated to 2.5 million tons annually worldwide since 1950., created a number of public and environment concerns. This book, organized in two sections, addresses the various aspects of the pesticides exposure and the related health effects. It offers a large amount of practical information to the professionals interested in pesticides issues.

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