子宮内膜症は様々な要因が複合して表現型を示す疾患であり,単一のSNPのみで子宮内膜症の疾患感受性を判断するのは不可能である.子宮内膜症の発症に関して内分泌撹乱物質の曝露量と遺伝子多型との関連性について解析した報告はこれまでのところなく,今後の研究課題の一つと考えられる.

今年になってダイオキシンの内分泌撹乱物質としての分子機構が初めて解明され,また子宮内膜増殖作用も実験的に確認された.この研究を契機として今後も内分泌撹乱物質の作用機序の研究が大きく進展していくと思われる.

おわりに

子宮内膜症の発生頻度の増加と内分泌撹乱物質との関係が疑われているが,現時点では明らかな因果関係の証明はされていない.内分泌撹乱物質の影響はグレーゾーンが広く,今後も1つ1つ新たな知見を積み上げてリスク評価を行っていくことが重要である.最近では子宮内膜症の患者で自己免疫疾患やある種の癌のリスクが高いことが報告されている.これらの新しい角度からの研究が子宮内膜症の病態解明に寄与し,効果的な治療法や予防法の開発につながっていくことが今後期待される.

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[Review]

Male Reproductive Health in Relation to Occupational Exposure to Endocrine Disrupting and Other Potent Chemicals, A Review of the Epidemiologic Literature

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Abstract: The line of research focusing on the human, especially male, reproductive system in relation to occupational exposure has diversified since the infiltration of the concept of endocrine disrupting chemicals (EDC), early in the 1990s. The main stream, until then, was the study of reproductive toxicity caused by single albeit relatively heavy exposures to chemicals of limited range (conventional scheme). The new and increasingly important stem is the search for a wider range of chemicals with endocrine disrupting potential, and health effects due to multiple low-dose exposures of potent chemicals (new scheme). There are also studies having aspects of both the conventional and new schemes. For studies with the new scheme, progress has been made in areas such as adherence to standardized techniques in evaluating male reproductive function and more sensitive study designs. Indeed, some studies have suggested the presence of EDCs in the occupational setting. However, epidemiological findings are still constrained by difficulties in the identification of occupationally-exposed populations and evaluation of exposure. There is thus a need for convergence of knowledge and a widening of the scope of epidemiological research targeting occupationally exposed populations under a carefully-designed protocol.

Key words: endocrine disrupter, occupational exposure, epidemiology, reproductive toxicity.

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Introduction

Endocrine Disruptors (ED) can be defined as "an exogenous substance that causes adverse health effects in an intact organism, or its progeny, consequent on changes in endocrine function" [1, 2]. The term, used interchangeably with "Endocrine Disrupting Chemicals

(EDC)", has infiltrated gradually into society, impacting scientists and the general public. In the field of occupational health, its penetration into the literature began around the early 1990s, particularly influencing the line of research on reproductive toxicology. However, there is a debate as to whether the introduction of the concept has had more benefits or drawbacks for the field, and this debate is likely to continue.

In view of the secular trend in the literature, the terms "pre- and post-introduction period" can be applied loosely to demarcate the periods before and after the early 1990s when the occupational epidemiologic research began to embrace the concept of EDC. A general observation can be made that, during the pre-introduction period, the scientific literature concerned with male reproductive health in relation to occupational exposure was discussed primarily in the context of a general process of reproductive toxicity. Subsequently, a view assuming a process mediated through EDC was introduced. However, for the related literature of that time, in the instances where EDC is not mentioned in a particular paper, it is difficult to discern the level of awareness and/or acceptance of the concept by the authors.

The objective of the present paper is to review the recent knowledge accumulated on the issue of male reproductive health in relation to occupational exposure. This review covers studies incorporating the conventional framework of reproductive toxicology, studies with a new framework probing into the emerging theme of EDC, and studies including both aspects. The ultimate aim is to overview the field of occupational epidemiology concerned with male reproductive health, and put into perspective its achievements, inherent problems and future directions.

To address the objectives of this paper, epidemiologic findings regarding the relationship between male reproductive health and occupational exposure are arranged according to the presumed biological endpoints: cancer of the reproductive tract, hormonal changes, reproductive function and offspring effects.

Cancers of the Male Reproductive Tract

Prostate Cancer

In 1994 the International Agency of Research on Cancer (IARC) designated cadmium as a class 1 carcinogen, but this pertained mostly to lung cancer. Occupational epidemiologic studies were not considered consistent in showing the risk for prostate cancer. Subsequently, in a 1994 review paper on cadmium and prostate cancer[3], a hormonal dependence of cadmium-induced prostate cancer was suggested from chronic exposure studies in rats.

Farming is by far the most often investigated occupation in relation to prostate cancer [4]. In a retrospective cohort study of farmers[5], herbicide spraying was identified as the specific exposure producing increased risk of prostate cancer mortality. The authors characterized the study as the first to have sufficient power to examine herbicide exposure and risk of prostate cancer. Excess mortality of prostate cancer was found in relation to occupational

exposure to coke oven emissions [6]. A meta-analysis[7]summarized that tire and rubber manufacturing had no relation to risk of prostate cancer. Several studies in an investigation of multiple occupations identified farming as a risk factor for prostate cancer. A case-referent study of 345 prostate cancer cases found farm laborers to be at risk[8], and later reviewed that farmers are at risk for prostate cancer(the actual exposure was not identified) [9]. A registry-linkage study[10]evaluated a wide range of occupations as risks for prostate cancer in Sweden, among which agriculture-related industries and occupations stood out as having a significant association(cadmium, herbicides and fertilizers were suggested as risk factors). None of the aforementioned studies implicated a hormonal mechanism.

A meta-analysis evaluating the link between prostate cancer and farming found positive associations[4], advancing that the hormonally active property of agricultural chemicals is the most plausible explanation. Subsequently, in a cohort study of more than 20,000 pesticide applicators, the risk of prostate cancer in terms of standardized incidence ratio(SIR)was calculated to be 1.13(95% confidence interval(CI)1.02−1.24) [11]. The authors discussed the possibility that the estrogenic activity of certain pesticides, *e.g.*, organochlorine compounds such as P, P'-dichlorodiphenyl trichloroetane(DDT), may affect the carcinogenic process. A case-referent study of prostate cancer showed that occupational exposure to diesel fuel or fumes, possibly mediated through polycyclic aromatic hydrocarbon(PAH), is associated with prostate cancer(odds ratio(OR)=3.7) (95%CI 1.4−9.8), but cadmium and herbicides are not [12]. Although EDC was not mentioned in this study, the authors postulated a hormonal effect with carcinogenic potential for PAH and other chemical constituents of diesel exhaust.

Fleming conducted a retrospective cohort study of licensed pesticide applicators and found that male applicators had an elevated mortality risk of prostate cancer(standardized mortality ratio(SMR)=2.38) (95%CI 1.83−3.04) [13]. This exemplifies an occupational epidemiological study with a firm framework of EDC: the authors noted that organochlorine pesticides may function as estrogen analogues as a possible explanation. An ecoepidemiologic study assessed the relationship between pesticide use and mortality from prostate cancer[14] at the Belgian municipality level but did not find any positive relationship.

Testicular Cancer

Studies that focus on the health effects of Agent Orange exposure among Vietnam veterans comprise an independent genre of literature. One example is a case-control study of testicular cancer patients in relation to surrogate exposures to Agent Orange, a phenoxy herbicide [15]. There were no positive findings to suggest that Agent Orange exposure is a risk factor for testicular cancer.

Swedish men were studied for possible associations between various occupations and the incidence of testicular cancer. Increased risk was found among metal workers, specifically related with seminomatous tumors, and among high socioeconomic groups, mainly related

with nonseminomatous tumors [16]. The authors found that although farming and military work are often reported to be positively related with the risk of testicular cancer, the two occupations were negative in the study.

A review paper of 1993[17]observed that testicular cancer had increased three- to four-fold since the 1940s and that this increase occurred worldwide regardless of the national level of frequency. Combined with observations such as the increase in congenital abnormalities of the male genitourinary tract(cryptorchidism and hypospadia)as well as the decreasing trend of semen quality and sperm density, the authors postulated a common etiological factor (*e.g.*, common hormonal mechanism)acting prenatally and/or postnatally. This paper is one of the earliest to consider in perspective various issues related to abnormalities of the male genitourinary tract. A review paper of 1998[18]recognized the increase in testicular cancer and purported a link between the growing number of "endocrine disrupters" (occupational exposure was not mentioned). A review by Moline *et al*. [19]provided excellent insights into the possible relationship between testicular cancer and EDC, with reference to occupational exposures. The use of pesticides atrazine and N, N-diethyl-m-toluamide, exposure to workplace hydrocarbon and PVC were designated as possible etiologic agents, while organochlorines such as DDT were characterized as "less likely". However, the authors cautioned readers to consider the established risk factors of testicular cancer(*e.g.*, cryptorchidism, Klinefelter's syndrome, hypospadias, infertility and disorders of other sexual gonadal development)and to "prioritize hazardous substances and elucidate the magnitude of male productive health effects."

The 1996 study on testicular cancer and parental use of fertilizers among Norwegian farm holders was conducted in view of the role of xenobiotics with estrogenic effects, a concept already advocated by that time. Among a cohort of male offsprings of farmers, the researchers found specific fertilizer regimens on the farm to be risk factors, especially for nonseminoma(rate ratio=4.21; 95%CI 2.13−8.32), but admitted the hypothesis-generating nature of the study. Hardell *et al*. [20]evaluated the relationship between risk of testicular cancer and occupational exposure to polyvinyl chloride(PVC), a substance rarely studied in relation to the EDC hypothesis. The case-control study conducted within the Swedish Cancer Registry showed an increased OR of 6.6(95%CI 1.4−32)for job exposure to PVC, which increased further if cases with self-reported cryptorchidism or orchitis were excluded. The study also showed that exposure to other types of plastics did not increase the risk of testicular cancer. Later the same authors corroborated the findings in a review paper[21], and added an interpretation that phthalates used in PVC as plasticizer have estrogenic properties that could promote the growth of endocrine sensitive tumor cells.

Hormonal Changes

Heavy Metals

Traditionally, heavy metal exposures have been the focus of many occupational epidemiologic studies, and some evaluated endocrine profiles as the primary end-point. Lead, mercury, chromium (hexavalent) and cadmium have been studied frequently *per se* or as an indiscriminant group of metals involved in welding [22], minting or glass production.

Lead is a reproductive toxin and has been frequently studied in connection with the endocrine function as a single end-point or in combination with fertility outcome. Examples of the former include a study showing that lead, at exposure levels frequently encountered in the occupational setting, increased follicle stimulating hormone (FSH) as a result of primary damage to the seminiferous tubules in the testes [23], and other studies [24, 25] showing no change in the level of FSH or luteinizing hormone (LH). These conflicting findings prompted a recent review to summarize that epidemiologic studies have been equivocal about the effects of lead on hormone concentrations [26]. A study of workers exposed to various metals concluded that even moderate exposures to lead can significantly reduce human semen quality without evidence of impairment of the male reproductive endocrine function [27]. It is noteworthy that this study hypothesized "endocrine-altering chemicals in the environment" as the underlying mechanism but ultimately refuted the possibility.

The epidemiologic relationship between occupational exposure to hexavalent chromium [Cr(VI)] and hormonal alterations have been evaluated in combination with sperm quality. An early study on welders concluded that low-level exposure to Cr(VI) associated with tungsten inert gas stainless steel and mild steel welding do not affect sperm parameters or serum concentrations of FSH and LH [28]. A more recent study on electroplating workers [29], in contrast, showed that Cr(VI) exposure reduced sperm count and motility (semen volume and liquefaction time did not change), increased the FSH concentration in serum, and implied that Cr(VI) may lower the reproductive potential of exposed workers. As regards mercury, workers exposed to its vapor (elemental form) did not show changes in pituitary hormone level (including FSH and LH) among subjects with documented levels of urinary Hg [30] or among subjects with documented levels of atmospheric exposure [31].

Cadmium merits particular attention among metals because it was recently designated as an endocrine disruptor by the U.S. Environmental Protection Agency [32], mainly because of its adverse effects on the reproductive system of wildlife [33]. A cross-sectional study of male workers was conducted at a smelter using creatinine-adjusted urinary cadmium (UCd) as the indicator of cadmium body burden and showed that the levels of serum testosterone and LH were significantly increased, but FSH was not changed among the exposed. It was thus suggested that the extent of Cd exposure may contribute to changes in serum reproductive hormone levels [32].

Organic Solvents

Toluene, a common organic solvent known for its neurotoxic properties, was examined for possible endocrine effects. Results from two independent examinations of male workers exposed to toluene in rotogravure printing companies were in accord, one showing decreased levels of FSH, LH and free testosterone relative to unexposed referents[34], and the other showing a dose-dependent decrease of FSH and LH [35]. The authors postulated a direct effect on the hypothalamic-pituitary axis rather than a secondary effect, through inhibition of the testis.

Trichloroethylene(TCE)is a common halogenated hydrocarbon used mainly as a solvent to remove grease from metal parts, which is also known for its hepatotoxicity. Chia *et al*. studied the endocrine profile of male workers with exposure to TCE, following their earlier findings of impaired spermatogenesis among TCE-exposed workers [36]. A dose-response decrease of serum FSH, testosterone and sex-hormone binding globulin(SHBG)with increasing years of exposure to TCE was found, suggesting "a disruption of peripheral endocrine function" "via the TCE-induced reduction of the liver production of SHBG." This supposition was later reinforced when analyses of insulin and adrenal hormones were performed in conjunction [37].

Other Chemicals

Exposure to carbon disulfide(CS_2)among viscose rayon workers was not associated with levels of FSH, LH or testosterone [38].

A long-term(longer than 17 years)follow-up of workers exposed to dibromochloropropane(DBCP)at levels severe enough to cause azoospermia or oligospermia resulted in high FSH and LH levels, reflecting permanent testicular damage. A similar mechanism of endocrine hormonal effects, secondary to testicular damage, was postulated in a study of male workers exposed to organophosphate pesticides(ethylparathion and methamidophos) [39].

Two subtypes(alpha and beta)of estrogen receptors(ER)have been identified in a study of the biological mechanism of EDC. It has been widely held that EDC affects reproductive processes primarily by altering estrogenic and antiandrogenic activities. A recent review paper, accounting for the widespread tissue distribution of ER, postulated ER as mediators of estrogen action [40]. In another recent review written in the context of reproductive toxicology, EDC was discussed as(not the sole but)one of the several future directions that warrants evaluation [41].

Hanaoka *et al*. [42]studied 42 male epoxy resin sprayers exposed to bisphenol-A and compared them with 42 matched non-exposed control workers. Sprayers showed lower concentrations of FSH than controls, which correlated with urinary bisphenol-A, while LH and free testosterone were not altered. The authors concluded that bisphenol-A may disrupt secretion of gonadotrophic hormones in men. This study was conducted with the specific objective to examine the effect of occupational exposure to suspected EDC, and, as such, may

prompt a new line of research.

Reproductive Function

Heavy Metals

There is controversy over how occupational exposure to lead poses a deleterious effect on male reproductive functions including sperm quality, fertility, or time-to-pregnancy (TTP). In the large body of literature examining sperm quality as the end-point, studies showing positive relationships are dominant. Lead-exposed males with biologically monitored exposure data showed lower sperm concentration [43], asthenospermia and teratospermia [44], abnormal morphology [45], and reduced sperm motility [46, 47]. Some studies showed this reduction to be proportional to blood lead level [46, 47]. One study suggested a positive relationship by demonstrating an improvement in sperm motility and penetration concomitant to a decrease of blood-level concentrations [47]. In contrast, studies showing negative relationships for morphology, sperm count or concentration [45, 48] are much fewer in number. The positive findings may be a direct effect of lead on reproductive organs, or on the endocrine control of reproduction, or both [44]. However, one study addressed the issue directly and concluded that even moderate exposures to lead can significantly reduce semen quality without impairment of male reproductive function [27].

Welding exposes workers to dusts and fumes containing metals, solvents and toxic gases [49]. Parameters of semen quality deteriorated (except for sperm concentration) among welders with a dose-response relationship in a cross-sectional [50] and longitudinal [51] study. In contrast, a study of Danish welders produced negative findings, although the authors cautioned against extrapolating the results to higher-level exposures [22].

Organic Solvents

A fairly wide range of evidence has been accumulated regarding the link between altered reproductive function and job exposure to organic solvents.

Occupational exposures to mixtures of benzene, toluene and xylene are common in the painting and printing industries. Male workers with long-term exposures showed deterioration of semen indicators, including sperm vitality, motility, acrosin activity and prolongation of liquefaction time, which may possibly affect pregnancy outcomes [52, 53]. The difficulty of isolating the effect of specific exposures from the effect of other concomitant exposures have been mentioned in a study of aircraft manufacturers [54] and infertile patients [55], and was regarded as a major problem in a review article [56].

2-Bromopropane was introduced as a substitute for chlorofluorocarbons (CFCs), and reproductive health effects were recently reported among male and female workers following an intoxication accident in an electronics factory of South Korea [57, 58]. Two out of eight male workers showed azoospermia and four showed some degree of oligospermia [57].

Carbon disulfide, the primary source of exposure among viscose rayon workers, showed no association with gonadotropin levels[38], but an accompanying paper reported decreased libido, loss of potency and in some cases, spermatic effects [59].

Ethylene glycol ethers constitute an important class of organic solvents in paints, printing inks and thinners [60]. Their use is widespread and spermatogenesis in animals has been well demonstrated [61]. Earlier studies of occupationally exposed males have produced mixed results [61]. A well-controlled case-control study did not find a correlation between the concentration of urinary metabolites and various measures of sperm quality [60]. However, it should be noted that glycol ethers are classified as a reproductive toxin by the European Union [49].

TCE and tetrachloroethylene (or perchloroethylene, PER) are solvents widely used as degreasers. TCE was replaced by PER in the dry-cleaning industries because it was considered less toxic [49]. Hyperzoospermia (sperm density of $>$ 120 million sperm/ml of ejaculate; implicated in infertility) increased with urinary metabolites of TCE among electronics factory workers[62] and subtle but dose-dependent effects on sperm quality were found for PER among dry cleaning workers [63]. A study of trinitrotoluene (TNT) exposed workers showed that, in addition to the decreased level of serum testosterone, semen volume and sperm motility deteriorated accompanied by impotence and loss of libido [64]. An association between exposure to aromatic solvents and reduced semen quality was demonstrated in a case-control study conducted at infertility clinics. The association was stronger if the case definition was based on stricter cutoff values for semen parameters [65].

Researchers at the National Institute of Occupational Safety and Health, USA, hypothesized that the stilbene derivative 4, 4'-diaminostilbene-2, 2'-disulfonic acid, an intermediate in the manufacture of fluorescent whitening agents, may have estrogenic properties based on structural similarity with estradiol and with the potent synthetic estrogen diethylstilbestrol [66]. Exposed male workers were found to have lower testosterone levels in a dose-dependent manner[66] and decreased libido and potency[67], thereby supporting the hypothesis.

Pesticides

The recent concern towards the male reproductive effects of pesticides is based on the increasing recognition that pesticides may not only exert direct cytotoxic effects on male germ cells but they may also act through subtle mechanisms such as disrupting the endocrine system [68]. In the last decade or so, many pesticides have thus been studied under the conventional framework of testis toxicity and/or a renewed framework of endocrine disruption.

DBCP exemplifies by far the best-documented pesticide causing testicular damage. The first report from an occupational setting was published in 1977, observing infertility among male pesticide production workers in California exposed to the nematocide 1,2-dibromo-3-chloropropane (DBCP) [69]. A preliminary study of five men showed that all were oligo-

zoospermic or azoospermic, and a further study among other exposed men showed an exposure duration-dependent effect on sperm counts and serum FSH and LH levels [70]. Later almost analogous incidents were reported from other occupational settings, including Israel [71]. The 1977 clinical observation has been recently characterized as "a sentinel event of major importance in occupational medicine [72]." Spermatogenesis recovered to only a limited extent among the affected workers [73]. It should be noted that a recent report of a large cohort of DBCP applicators in developing countries revealed azoospermia or oligospermia in alarmingly high proportions [74], which has attested to the spread, rather than the solution, of the DBCP problem.

Although there is a wide range of chemicals used as pesticides, it is important to recognize the paucity of epidemiological data in comparison to the amount of experimental data available [68]. Accordingly, *in vivo* experimental data have provided the basis for designation of EDC. In Italy, for example, out of the 352 active ingredients registered for agrochemical products, 34 have been defined as endocrine disruptors [68, 75]. In this regard, occupational epidemiologic studies assume an important role to investigate associations in the human population and generate new hypotheses. In the past decade or so, the following studies have added insights to the possible association between occupational exposure to pesticides and male reproductive function.

Farm sprayers exposed to 2, 4-dichlorophenoxyacetic acid showed significant levels of asthenospermia, necrospermia and teratospermia, and the effect persisted for teratospermia[76]. Time to pregnancy(TTP), defined as the time interval between the start of unprotected intercourse and a clinically recognizable pregnancy[77], has been increasingly utilized as an endpoint of infertility [78−80]. TTP was delayed among fruit growers exposed to pesticides that could not be specified, producing a fecundability rate ratio of 0.46(95% CI 0.28−0.77) relative to the referent group [78]. (Similarly, greenhouse workers were at increased risk of increased TTP among workers with high exposure [80].) In contrast, TTP was not affected among farmers and greenhouse workers exposed to pesticides when compared with organic and conventional farmers not exposed to pesticides [79].

There is also an array of studies showing negative results. A study of sawmill workers exposed to cholorphenate fungicides and their dioxin contaminants showed little evidence for reduction in fertility [81]. A study of farmers exposed to fungicides and other pesticides showed no association with sperm aneuploidy [82]. Each study revealed inherent problems that may have led to spurious effects, *i.e.*, confounding by time since hire in the former and the positive effect of smoking in the latter. A study on production workers of molinate, a thiocarbamate herbicide used for weed control in rice fields, showed no effect on sperm or serum hormone levels [83]. One study tested the hypothesis of whether semen quality, assessed by the WHO criteria, differed between traditional farmers and organic farmers, and concluded that there was no difference [84].

The following studies, published during the same period as above, have suggested positive

relationships between occupational pesticide exposure and male reproductive function. Pesticide factory workers in China exposed to ethylparathion and methamidophos exhibited sperm aneuploidy (rate ratio of 1.51) [85] and reduction of sperm concentration and motility [86], suggesting a moderately adverse effect on semen quality. Danish researchers studied greenhouse workers with known exposure to more than 60 pesticides under the framework of endocrine disruptors. The high-level exposure group showed lower sperm concentration, morphology and viability under WHO guidelines [87]. A study was conducted on Mexican males exposed to DDT spraying for malaria control, despite the cease of its use in industrialized countries. The body burden of DDT metabolite was inversely correlated to semen volume and sperm count [88]. Such findings raise concern on the situation of developing countries, similar in nature to the report on DBCP.

Offspring Effects

For this section, the offspring effect can be defined as an endpoint that can be evaluated among the offspring of the occupationally exposed male, *i.e.*, paternal exposure. The offspring effects include changes in the sex ratio, cancer, accelerated puberty, and among males, cryptorchidism (undescended testis) and hypospadia. The central question to be addressed here is whether a common etiology exists among the offspring effect and other effects including reproductive function, hormonal changes and cancer among the exposed. Testicular dysgenesis syndrome [89] is the specific terminology applied in instances where only the exposure and effects among males are considered, and a common etiology is hypothesized for hypospadias, cryptorchidism, testicular cancer and infertility [19]. In particular, cryptorchidism and hypospadia have been characterized by Sharpe and Shakkebaek [1] as "representing mild degrees of feminization", and "important in the ongoing debate regarding the significance of endocrine disruptors or other environmental influences on male development".

Many researchers have argued that the incidence of cryptorchidism and hypospadia increased over the years in many countries [17, 18, 90, 91]. Although the secular trend certainly merits investigation, the reservations expressed in accompaniment with such observations are important. The reservations include the ethnic and racial differences in the underlying rates, inconsistencies in diagnostic procedures and criteria [17, 18] and inefficiencies with reporting [17]. This is particularly true with cryptorchidism, because the defect resolves spontaneously by the first birthday in $> 70\%$ of affected infants [19]. There is a contradictory observation that the rates of these diseases may, in fact, have decreased [92]. The issue is thus still inconclusive, but the possible increase of cryptorchidism and hypospadias as an effect of EDC cannot be dismissed. It is not only theoretically possible but can be deduced from the increased rate of cryptorchidism and hypospadia observed in the sons of women treated with the synthetic estrogen diethylstilbestrol [93].

Whereas the number of papers on temporal analyses is abundant, few studies have directly

evaluated the risk of cryptorchidism and hypospadia. Cryptorchidism rates (evaluated by orchidopexi rates) tended to be higher in districts where intensive farming is widespread [94]. The risk of cryptorchidism was significantly increased among the offspring of female (but not male) gardeners [92, 95]. Another study inferred a causal relationship between hypospadia and maternal occupational exposure to EDC [96]. In a recent case-control study from China, risk factors for cryptorchidism were sought, and paternal exposure to pesticides emerged with an OR of 12.8 (95% CI 2.9−56.4) [97].

Sex ratio and testicular cancer of offspring have been evaluated as an end-point in several observational studies. A predominance of female offsprings have been observed in relation to paternal exposure among Israeli DBCP production workers [71], Seveso accident survivors exposed to 2, 4, 5-trichlorophenol [18, 98] and glass workers [99], but such a relation was negated in a study of male employees exposed to inorganic borate compounds [100]. While one study showed an increase of testicular cancer in the offspring of farmers' sons (notably non-seminoma) [101], another study found no association between parental occupation in agriculture and testicular cancer in the offspring [102].

In conclusion, although it is often difficult to draw a distinct line between an endocrine disrupting process and a more general toxicological process, some occupational epidemiologic studies have begun to implicate the presence of EDCs in relation to the risk for cancer of the reproductive tract, hormonal changes, reproductive function and offspring effects. Progress has been made in areas such as adherence to standardized techniques in evaluating the male reproductive function and more sensitive study designs. However, epidemiologic findings are still constrained by difficulties in the identification of occupationally-exposed populations and the evaluation of exposure [103]. There is thus a need to combine knowledge from related disciplines and widen the scope of epidemiologic research targeting occupationally exposed populations under a carefully-designed protocol.

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