REVIEW

Is Environmental Exposure Associated With Reproductive Health Impairments?

Sunil **KUMAR**

Division of Reproductive Toxicology, National Institute of Occupational Health, Ahmedabad, India

Received 27 April 2007; received in revised form 25 September 2007; accepted 01 October 2007; published online 10 March 2008

Abstract

All living beings and even non-living things are exposed to various exogenous as well as environmentally persistent chemicals through different routes. Thousands of tons of synthetic chemicals are produced worldwide annually. Upon being released into the environment, they persist for decades. Many of them identified as endocrine-disruptor chemicals (EDCs) have hormone-mimicking properties and might affects on the fertility of different species. Evidence has steadily accumulated in recent decades of the detrimental effects of the EDCs released to the environment on the reproductive health and related outcomes, such as, deterioration of semen quality, increase incidence of cryptorchidism, hypospadias, and testicular and prostate cancer in the male and a rising trend of breast cancers, and endometriosis (a disease where uterine endometrial tissue grows outside the uterus), menstrual disorders, etc in the female, and increasing genital defects in both sexes. There are reports mostly from animal studies including those in the wild life that exposure to EDCs while in the uterus may harm the fetus and lead to anomalous development of reproductive organs resulting in subfertility. There is need to program well controlled studies to correlate the chosen effect parameters with the exposure level in order to obtain specific information on the chemicals responsible for these adverse effects and plan the measures to be taken to reduce exposure.

Keywords: environmental chemicals, semen quality, cryptorchidism, endocrine disruptor chemicals (EDCs), endometriosis

Özet

Çevresel Etkenlere Maruziyet Üreme Sağlığının Bozulması ile Bağlantılı mıdır?

İnsan dahil bütün canlılar, bedenleri dışında ve doğada kalıcı çeşitli kimyasallara değişik yollardan maruz kalmaktadır. Dünyada her yıl binlerce ton yapay kimyasal üretilmektedir. Bunlar, doğaya bırakıldığında uzun yıllar varlıklarını sürdürmektedir. Birçoğunun hormon karşıtı özellikleri olup değişik tür varlıkların üretkenliğini etkileyebilir. Erkek cinste sperm kalitesinde bozulma, kriptorşidizm olaylarında artma, hipospadiyas ve testis ve prostat kanserleri ve kadınlarda meme kanserleri olaylarında artış, endometriyozis (rahim endometriyum dokusunun rahim dışında gelişmesi), menstrüasyon düzensizlikleri ve her iki cinste de cinsel organ bozuklukları gibi üretkenlikte artan bozulmaların, doğada birikmiş atık kimyasallardan kaynaklandığına işaret eden kanıtlar son senelerde çoğalmıştır. Genellikle, vahşi olanlar dahil, hayvanlar üzerinde yapılan çalışmalarda rahim içinde iken kimyasallara maruz kalmanın fetüse zarar verdiği, cinsel organların anormal gelişmesine ve üretkenliğin azalmasına neden olduğu bildirilmektedir. Maruz kalma süresi ve şiddeti karşılaştırılarak, bu istenmeyen etkili kimyasallara özgü bilgi toplanarak, korunma çareleri saptamak için iyi planlanmış çalışmalara gereksinim bulunmaktadır.

Anahtar sözcükler: doğada kimyasallar, sperm kalitesi, kriptorşidizm, endokrin olayları bozucu kimyasallar, endometriyozis

Introduction

All living and even non-living beings are exposed to numerous chemicals persisting in the environment. The scope of the reproductive disorders thus caused in the general population is becoming widely documented, and the possible role of these agents present in the environment on the incidence of these disorders has renewed worldwide attention to review the problem. There is concern in the scientific community and the public about commonly used chemicals that are hormonally active and potentially toxic to reproductive systems. There has been growing apprehension that synthetic chemicals released into the environment have affected the development and/or function of the reproductive, endocrine, immune and nervous systems of different species, including the wildlife fauna. To this date, only a few of the many persistent chemicals have been screened for their

Corresponding Author: Dr. Sunil Kumar
Division of Reproductive and Cytotoxicology, National Institute of Occupational Health, Ahmedabad 380016, India
Phone : +91 079 226 86 351-352
GSM : +94 263 957 38
Fax : +91 079 226 86 11
E-mail : sunilnioh@yahoo.com

endocrine disruptive activity. Exposure of humans to these chemicals appear to be related to various reproductive health problems such as reduced fertility, menstrual disorders, impaired spermatogenesis, cryptorchidism and hypospadias, pregnancy loss, low birth weight, structural and functional birth defects, post natal developmental defects etc., without conclusive evidence. The biological exposure monitoring data along with appropriately chosen parameters of the adverse effects (effect parameters) are scanty to provide specific information on the chemical and other factor responsible for the reproductive impairments observed. Further, confounding factors such as malnutrition, infections, smoking and chewing tobacco, indoor pollution, etc. may also be involved in reproductive dysfunction.

Materials and Methods

This overview is mainly about data available on the adverse effects of environmental and occupational exposure to chemicals on human reproductive functions and also about the relevant data on the 'environmental endocrine disruptors' (ECDs). Some references related to observations on wild life species have also been integrated whenever necessary. The literature was accumulated through searching various databases such as Pub Med, Medline and certain other websites as well as consulting various journals specifically related to occupational, environmental and reproductive health. The results based on different studies related to reproductive impairments in the male and the female are summarized in Tables 1 and 2.

Endocrine disruptor agents and reproductive health

A number of animal species in the wild life have shown signs of abnormal sexual development and growth, such as deformed genitalia, aberrant mating behavior, sterility, infertility and other physical and behavioral anomalies which scientists have linked to the EDCs. These chemicals interfere with the biochemical signals that guide development before and after birth. They are passed from mother to offspring, affecting the growth and development of the offspring. Effects of exposure *in utero* to very low doses of these chemicals may be seen in early life and adulthood in the form of reduced fertility or other health disorders. This can be detected in the exposed individuals when attempting pregnancy and on the outcomes of these pregnancies. Hormones are important for the proper development of the growing fetus and neonate as well as having vital effects on reproductive cells, pregnancy and lactation. The developing offspring is the most sensitive target of endocrine disruption since much of the neural, reproductive, and immune development occurring in the womb continues up to early childhood (1). It is understood that organ development is put to particular risk with maternal exposure to these chemicals. Developmental abnormalities seen in the offspring include the receptors for gonadal hormones such as those in the prostate, seminal vesicles, epididymes and testes in the male fetus; as well as those in the mammary glands, fallopian tubes, uterus, cervix and vagina of the female fetus. In both sexes the external genitalia, brain, skeleton, thyroid, liver, kidney and the immune system are also targets for the EDCs (2-4).

Table 1. Reproduction dysfunction in males and the male-mediated reproductive outcome

Metal	Reported effects
Lead	Impaired reproductive function by reducing sperm count, motility, and normal morphology[37]
	Impairment of spermatogenesis[38]
	Reduced semen quality[42]
	Decline in sperm motility and viability[43]
Mercury	Reduction in sperm count and terato and asthenozoospermia[51]
	Impairment of fertility index[52]
Chromium	Changes in semen quality and reproductive hormones[58]
	Deterioration in sperm morphology[59]
Cadmium	Inverse correlation between blood Cd and sperm density[61]
Pesticide (single or number of pesticides)	
Di-bromo chloropropane	Reduction in sperm concentration, and infertility[71,72]
	Atrophy of the seminiferous epithelium[73]
	Elevated level of serum LH and FSH and reduced sperm count[75]
Carbaryl	Deterioration of sperm morphology[76]
2,4-dichloro phenoxy acetic acid	Asthenozoospermia and teratozoospermia[77]
Multiple pesticide exposure	Male mediated adverse reproductive performance[78]
Paternal exposure to pesticide	Associated with cryptorchidism[15]
Solvent	
2-ethoxy ethanol exposure during painting	Lower total sperm count[90]
Ethylene dibromide	Decrease in sperm motility and viability[91]
Carbon di-sulphide	Higher frequency of asthenospermia, hypospermia and teratospermia[92]
	Significant effect on libido and potency[94]
	No significant changes in sperm count and morphology[95]
2-bromo- propane	Oligospermia and azoospermia[107]
Styrene	Oligospermia and azoospermia, sperm count decline[100]
Phthalate esters	
Mono butyl and mono benzyl phthalate	Changes in sperm morphology, motility and concentration[115]

Table 2. Reproduction dysfunction in the female

Metal	Reported effects
Mercury	Stored in pituitary gland and affects the production of gonadotropins in primates[67] Less fertile[53]
Lead	Increased risk of low birth weight and neural tube defects[49] High blood Pb level with pre-term delivery, spontaneous abortion[48]
Cadmium	Preterm infants with high Cd in blood[64]
Elevated heavy metals body load	Greater risk of miscarriages, fetal malformations, premature births[64-66]
Pesticide (single or multiple pesticides)	
Multiple chemical/pesticide exposure	Casual association of cryptorchidism with occupation among sons of female gardeners[14]
Multiple pesticide exposure	Higher abortion[82]
Exposed to pesticides during first trimester of pregnancy	Small for gestational age[83]
Maternal pesticide exposure	Spontaneous abortion[81]
Maternal serum DDE level	Increased risk of spontaneous abortion[85]
Maternal serum DDE level	Increased risk of pre-term delivery[84]
Solvents	
2-bromo propane	Ovary dysfunction accompanying amenorrhea[107]
Carbon disulphide	Early menopause and reduction of serum concentration of estrone, estradiol, progesterone, 17-hydroxyprogesterone[96] Increase incidence of spontaneous abortion[97,98] No relationship between CS_2 concentration and miscarriage[99]
Exposure to organic solvent in petrochemical industry	Maternal exposure lead to reduced birth weight[102]
Exposure to ethylene glycol ether	Increased risk of spontaneous abortion Female sub fertility[89]
Toluene	Reduced fecundity[109]

Exposure to very small amounts of EDC at a critical period of the development of the fetus or the infant can be more harmful than greater exposures at other times or during adulthood. Fox reported that in the Lake Ontario area, USA; a region highly contaminated with DDT, newly-hatched herring gull chicks presented altered reproductive systems. Male chicks had oviducts and gonads resembling ovaries and the oviduct system of female birds had developed abnormally (5). Reduction in penis size and serum testosterone levels in the juvenile alligator population of Lake Apopka, Florida, USA, have also been attributed to the contamination of the lake by the DDT-metabolites p,p–DDE and p,p–DDD (6). Later the same group of investigators also drew attention to the two nematocides, dibromochloropropane (DBCP) and ethylenedibromide (EDB), that are established reproductive toxins in humans, which could also have played a role in the reproductive failure observed in the alligators of Lake Apopka in the early 1980's (7). DDE has also been identified as the principal pollutant causing eggshell thinning and reproductive failure in predatory birds. Even though DDT has been banned in many countries, there are incidents when DDE levels in bird's eggs and the prey species around the world are still high enough to cause reproductive failure (8). Now it has been realized that some of the endocrine-disruptive effects, previously thought to be estrogenic, are in fact due to anti-androgenic effects. Several environmental chemicals including metabolites of the fungicide vinclozolin and the pesticide DDT disrupt male reproductive development and function by inhibiting androgen receptor-mediated events (9). These chemicals commonly bind the androgen receptor with moderate affinity and act as antagonists by inhibiting transcription of the androgen dependent genes. Yu et al. (10) published the data on the people poisoned by cooking oil contaminated with heat-degraded polychlorinated biphenyls (PCBs). They interviewed the exposed women and suggested that high level exposure to PCB and polychlorinated dibenzofuran (PCDF) has adverse effects on female endocrine and reproductive function. It has been reported that women in industrialized countries reach puberty (menarche) earlier and may experience menopause later. Lactation is often of much reduced frequency and duration. In addition, the incidence of some reproductive cancers is increasing, including breast cancer and vaginal/cervical cancer. The incidence of endometriosis is also increasing while the age of onset is decreasing (11). It is possible that many of these conditions may be associated with exposure to high levels of EDCs, particularly the oestrogenic chemicals, during development or in adult life (12,13). Weidner et al. (14) reported a significantly increased risk of cryptorchidism among the sons of women working in gardening, suggesting an association with prenatal exposure to occupationally related chemicals. However, risks were not increased in sons of men working in farming or gardening. Later Pierik et al. (15) argued that paternal exposure to pesticide was associated with cryptorchidism. Smoking by the father was associated with hypospadias. However, exposures through maternal occupation or diet and life style were not found to be associated with either anomaly.

Burning of chlorine-contaminated waste creates dioxins, ranked among the most toxic chemicals ever identified. Dioxin from incinerator smokes can travel through the air on dust or water particles and eventually fall to the ground; sometimes as far as hundreds or thousands of miles away from the source (16). Small quantities which bio-accumulate in the body fat of the feeding animals is passed on to humans via food chain. For example, when people eat meat or dairy products, they also consume some of this dioxin. US Environmental Protection Agency (EPA) estimates that 90% of human dioxin exposure comes from food (16). Yonemoto, having reviewed the effects of dioxin on reproduction and development, has reported that experimental exposure of animals to dioxin during pregnancy and lactation induces various functional effects on offspring at a very low doses. Dioxin in human breast milk might affect thyroid function in the infants (17). Occupational exposure to dioxin may lead to adverse effects on the adult male reproductive system. One example to the adverse effects of dioxins on the adult male reproductive system is the observation of reduction in the testicular size of some of the men who participated during the Vietnam War in the aerial spraying of the Agent Orange contaminated with dioxins. The effect correlated with dioxins levels in their blood (18). A recent study on chemical industry workers exposed to dioxins has reported decrease in testosterone and increases in follicle stimulating hormones (FSH) and luteinising hormone (LH) levels which significantly correlated with dioxin levels in blood (19). International Program on Chemical Safety (IPCS) has documented that dose–response relationship is the most controversial issue with regard to EDCs (20). A recent workshop on this topic concluded that although low-dose effects may be taking place, often they are not reproduced consistently, and the toxicological significance of the reported effects is not known (21). The observed adverse effects of EDCs in human and wildlife are limited to data mostly from highly exposed populations.

Semen quality, persistent environmental pollution with chemicals and the EDCs

There have been several recent reports on the decline of human sperm counts over the last few decades. Workers from different parts of the world and particularly from the western countries have observed an apparent drop in semen quality (22,23) which have stimulated further research. Carlsen et al. (23) have also published studies showing a significant decrease in sperm concentration and semen volume over 1938-1990. Mehta and Anand Kumar from Bangalore, India also reported a decline in semen quality (24). They correlated these changes with various air pollution indices like suspended particulate matter, sulphur dioxide and lead. However, other investigators (25,26) have found no changes in semen quality, spurring intense scientific debate. IPCS also has stated that a global trend for declining semen quality is not supported by the current data (20). Swan et al. mentioned that there was no evidence of a decline in semen quality in non-western countries while they observed a significant decline in Europe and the United States (27). Recently Orejuela et al. emphasized that generalization of a world wide declining trend of semen quality is still risky and highlights the need for innovative new prospective studies with good quality data to address this important issue of human reproduction (28). Some studies show declines in certain regions or cities, whereas others have not found a decline, suggesting there may be regional trends but not a global trend (20).

Sharpe and Skakkeback have postulated that apparent drop in sperm count may be due to the developmental exposure to estrogenic xenobiotics (29). Guo et al. studied the reproductive function of boys who were exposed prenatally to polychlorinated biphenyls and dibenzofurans. They reported that sperm of these exposed boys have increased abnormal morphology, reduced motility, and reduced capacity to penetrate hamster's oocytes (30). Skakkeback et al. proposed a new concept that poor semen quality, testicular cancer, undescended testis and hypospadias are symptoms of one underlying entity, the testicular dysgenesis syndrome (TDS), which may be increasing due to adverse environmental influences. Further, they suggested that TDS is a result of disrupted embryonic programming and gonadal development during fetal life (31). Recently, Massaad et al. proposed several possible mechanisms for the toxicity of xenobiotics that display hormonal activity and they have suggested that contamination by these compounds could occur at periods of development when the natural hormones are not secreted or are inactive. This could lead to an illegitimate activation of hormone receptors at the wrong time or place, and thus trigger developmental malformations (32). Hence, it can be assumed that exposure to EDCs might have little effect on the adult organism, but the offspring of that organism may suffer. This hypothesis remains to be probed by further studies.

All the available data suggest that EDCs can act at multiple sites via multiple mechanism of action. Denzo suggested that the weak hormonal activity of these chemicals can be augmented by interaction with more than one steroid sensitive pathway. He reported that numerous potential agonists/antagonists working together through several steroid–dependent-signaling pathways prove to be hazardous to human reproductive health (33). Recently, Aoki suggested that humans are exposed to dioxins from the environment along with various other compounds, e.g. polyaromatic hydrocarbons and heterocyclic amines, act synergistically, suggesting the possible enhancement of the endocrine disrupting activity of the dioxins by other environmental contaminants (34).

Evidence from wildlife on the hormone mimicking or antagonizing actions of EDCs in the intact animal is limited. Laboratory studies have shown only in a few cases that chemicals which mimic hormones at the molecular level *in vitro* also cause reproductive dysfunction *in vivo* at the environmentally relevant concentrations. The reported studies on wildlife population of animals are also limited to a very few animal species centering on localized hotspots of chemical discharge (35). Very recently, Vidieff and Sever reported that the results do not support with certainty the view that environmental

estrogens contribute to an increase in male reproductive disorders; neither do they provide sufficient grounds to reject such a hypothesis (36).

The overall functioning of the reproductive system is controlled by the nervous system and the hormones produced by the endocrine glands. The reproductive neuroendocrine axis of males involves principally the CNS, the anterior pituitary and the testis. Toxicants that damage the Leydig cells can lead to reduced secretion of testosterone, which in turn affect the Sertoli cell function and spermatogenesis. Most of the reproductive toxicants are thought to act directly on the testis. However, there are some indications that substances interacting with the pituitary secretion of gonadotropin (FSH, LH) and hypothalamic neuroendocrine releasing factors may also play an important role in semen quality. More conclusive data are needed to establish the mechanisms of reproductive dysfunction in humans and in wildlife fauna.

Environmental and occupational exposure to chemicals and reproduction

Metals and reproduction

General population is exposed to different metals and their oxides through the environment. Except lead, detailed studies on human reproduction with reference to heavy metals are scanty. However, the effect of heavy metals such as mercury, lead, cadmium, chromium etc. on male and female reproduction has been studied in detail in various experimental animal species and data on humans are steadily building up. Epidemiological studies have indicated that occupational exposures to lead have adverse effects on human sperm. Apostoll et al. reviewed the literature on toxicity of lead in reproductive system of male humans and animals. Lead levels above 40 µg/dl in blood impaired male reproductive function by reducing sperm count, volume, and density or changing sperm motility and morphology, but no related effects were detected on the endocrine profile (37). Telisman et al. concluded that even moderate exposure to Pb (Blood Pb <400 µg/L) and Cd (Blood Cd <10 µg/L) could significantly reduce human semen quality without conclusive evidence of impairment of male reproductive endocrine function (38). In a cross sectional study among men employed at a lead smelter, blood lead concentrations below the currently accepted workers' protection criteria seemed to adversely affect spermatogenesis (39). The mechanisms by which semen quality is altered by exposure to lead is unknown. Benoff et al. reported that lead (Pb_2+) and cadmium (Cd_2+) accumulate in male reproductive organs and genetic polymorphisms as in somatic diseases might modulate Pb_2+ and Cd_2+ related damage. Multiple calcium (Ca_2+) and potassium (K+) channel isoforms have been identified in human testes and spermatozoa. These Ca_2+ and K+ channels are involved in early events of acrosome reactions. Ca_2+ channels are susceptible to Cd_2+ poisoning and K+ channels to Pb+ poisoning. These channels offer entry paths for metallic toxicants into mature spermatozoa. Ion channel polymorphisms may cause differential sensitivities to Cd_2+ and Pb_2+, explaining in part the prospective blinded studies showing high Cd_2+ in varicocele-related human infertility and high Pb_2+ in unexplained infertility (40). Lead levels were found to be negatively correlated with sperm function biomarkers and positively correlated with the spontaneous acrosome reaction such that increased lead levels might contribute to the production of unexplained male infertility (41).

Dawson et al. compared sperm viability with metal levels in seminal plasma of apparently healthy men. Significant differences were observed between the groups with high and low live sperm counts for Pb ($p \leq 0.01$) and Al (0.05) but not for Cd. Further, linear regression between the live sperm counts and level of the three metals in semen showed inverse correlation with the percentage of live sperm and metal level (42). Recently a study carried out among traffic policemen in Peru where leaded gasoline is still used indicated that sperm motility and viability decreased significantly with increasing Pb levels in simple linear regression (43). All the available studies clearly suggest that blood lead level nearly 40 µg/dl might have adverse effects on spermatogenesis (44). However, adverse effects of exposure to lower level of lead on semen quality cannot be ruled out. Recently it has been reported that zinc and α glucosidase activity levels were lowest among the azoospermic in comparison to the oligozoospermic and normospermic and a positive correlation was observed between zinc level and sperm count and zinc and α glucosidase activity in seminal plasma (45). The available data suggest that zinc and α glucosidase seem to play an important role in human male reproduction.

There is less data on the effects of lead on female reproduction. Lin et al. found no significant differences in the birth weight and pre-maturity/gestational age of the offspring of fathers occupationally exposed or not exposed to lead. However, workers with elevated blood lead levels for more than 5 years had a higher risk of fathering a child with low birth weight or prematurity than did the unexposed controls (46). Daniell reported that painters and construction workers assumed to have been exposed to lead and solvents during work also show adverse effects on both male and female reproduction (47). A mean blood lead level of 22.52 µg/dl was observed among pregnant women with various adverse outcomes such as pre-term delivery, stillbirth and spontaneous abortion as compared to 19.4 µg/dl in normal delivery cases (48). Irgens et al. observed that offspring of mothers occupationally exposed to lead had an increased risk of low birth weight and neural tube defects however; offsprings of fathers exposed to lead had no increased risks in any of the analyzed reproductive outcomes (49). Further, Shiau et al. investigated the time to pregnancy (TTP) in male battery workers exposed to lead and observed a dose-response relationship between blood lead levels and TTP (50). These studies suggest that lead has adverse effect on the reproductive system of both sexes. However, further studies are needed to find out the lowest level of lead at which reproductive toxicity occurs in both sexes.

Mercury is also known to have deleterious effects on reproduction. However, evidence is limited and the sample size

has been small in most of the studies. Occupational exposure to alkyl mercury has been reported to cause reduced sperm counts and terato and asthenozoospermia (51). In another study on men occupationally exposed to mercury, the observed impairment of the fertility index was associated with seminal mercury concentrations ten times higher than that in the serum (52). Rowland et al. reported that women with high occupational exposure to mercury were less fertile than unexposed controls (53). A study among the wives of 152 workers occupationally exposed to mercury vapour and 374 control subjects indicated an increase in the rate of spontaneous abortions with an increasing concentration of mercury in the father's urine before pregnancy (54). Data of a survey among dental professionals in USA showed little, if any alterations in the risk of spontaneous abortions for female dentists working with amalgam and nitrous oxide (55). Schuurs reviewed the work on occupational mercury exposure and reproductive toxicity and suggested that more research is needed concerning the effects of occupational elemental mercury concentrations lower than the threshold limited value (TLV) on the menstrual cycles, conception, male fertility and children's behavior (56). Mercury might affect the normal development of the offspring including the reproductive system as it has been reported that after experimental inhalation of the mercury vapour by animals, Hg was found to be distributed to all maternal and fetal tissues in a dose-dependent manner (57).

Chromium has also been indicated to partake in reproductive dysfunction by data on humans and experimental animals. Occupational exposure might lead to changes in semen quality and reproductive hormone levels (58). Non-significant alteration in sperm concentration, motility, and viability has been reported in workers exposed to chromium together with significant increase in abnormal sperm morphology associated with the blood chromium levels (59). Data on the toxic potential of cadmium on reproductivity is also available. A significant inverse correlation between blood cadmium levels and sperm density among oligospermic men; and between seminal plasma cadmium and semen volume among men without known occupational exposure to cadmium have been reported (60). A significant inverse correlation was also found between Cd levels and sperm density, and sperm numbers per ejaculum among non-smokers, which indicated that Cd in seminal plasma could affect semen quality and oxidative DNA damage in human spermatozoa (61). Higher levels of cadmium have been reported in infertile men compared to fertile men (62). However, Mason did not find any differences in the serum testosterone, FSH and LH levels of men exposed to cadmium and the unexposed controls (63). The mean blood concentration of Cd in mothers delivered of pre-term infants was found to be higher than that of women who went to full term in an area with high amounts of lead and cadmium in the soil (64).

It has been suggested that pregnancies that occur despite an elevated heavy metal body load are at a greater risk of miscarriage, foetal malformation, placental insufficiency and premature birth (64-66). Danscher et al. reported that a number of harmful substances such as mercury are stored in the pituitary gland and affect the production of gonadotropins, which in turn may affect the reproductive function (67). The hypothalamic-pituitary-ovarian axis could be affected by heavy metals either directly or indirectly through modifications of the secretion of prolactin, adrenocortical steroids or thyroid hormones (68) and hormonal and immunological alterations induced by heavy metals might be important factors in the pathogenesis of repeated miscarriages (69). These data suggest that heavy metals might have effects on the ovary as well as hormone production and release. However, more data are needed to reach firm conclusions.

Exposure to pesticides and reproduction

Large numbers of workers engaged worldwide in the agricultural sector, or the pesticide industry are being exposed to various pesticides through different routes together with a sizeable number of their family members. The general population is also exposed to some extent to pesticides or their metabolites through the food chain. United Nations Environment Protection (UNEP) reported that nine of the twelve most unwanted persistent organic pollutants (POP's) are pesticides. Twelve POP's have been identified by the UNEP as a powerful threat to the human and wildlife health on a global basis (70). The toxic effects of the pesticide 1,2-dibromo-3-chloropropane (DBCP) on reproductivity have been well documented. Its spermatotoxicity in rats was discovered in the earlier 60's; and deleterious effects on human spermatogenesis in 1977 (71). Occupational exposure to DBCP caused reduction in sperm concentration in ejaculates from a median value of 79 million cells/ml in the unexposed men to 46 million cells/ml in exposed workers (72). Complete atrophy of the seminiferous epithelium was observed in six workers exposed to DBCP in a pesticide factory in Israel (73); which might possibly be responsible for the increase in spontaneous abortions experienced by their wives. The incidence of spontaneous abortion was 19% among women married to the DBCP workers as compared to 6.6% among those married to non-exposed workers (74). Elevated serum concentrations of LH and FSH and reduced sperm counts in male workers employed for DBCP production have been attributed to DBCP action upon the Leydig cells, altering androgen production and action (75). These studies suggest that DBCP has toxic effects on endocrine and reproductive functions in males.

Pesticides; like carbaryl, 2,4-dichloro phenoxy acetic acid and endosulphan, DDT, are also toxic to the reproductive system. Harmful effects of the carbamate pesticide carbaryl on sperm morphology has been reported (76). Significantly higher level of asthenozoospermia and teratozoospermia were found in workers engaged in spraying 2,4-D (2,4-dichloro phenoxy acetic acid) as compared to unexposed subjects (77)**.** There are only few studies on the reproductive systems of humans exposed to more than one type of pesticide. In India male workers who were exposed to groups of pesticides like organochlorines, organophosphates, synthetic pyrethroids during mixing and spraying showed male-mediated adverse reproductive performance such as abortion, stillbirths, neonatal deaths, congenital defects etc. (78). Pines et

al. (79) observed that males who had fertility problems generally had higher levels of organochlorines in their blood than the control group. Significant increases in DDT, DDD and DDE, as well as lindane and some tetra and penta-PCB levels had been estimated.

Epidemiological studies among agricultural and chemical industry workers have shown positive correlation between exposure to pesticides and reduced fertility among men and women, as well as spontaneous abortions, birth defects and other adverse pregnancy outcomes (78,80-83). Increased spontaneous abortion caused by direct maternal exposure to pesticide has been reported (81,82). Women exposed to pesticides during the first trimester of pregnancy had an increased risk of giving birth to babies that were small for gestational age (83).

Recently, strong positive correlations between the DDE levels in mother's blood and the probability of pre-term deliveries as well as the reduced birth weight of the infant have been reported (84) confirming the results of another case control study showing the increased risk of spontaneous abortion with elevated maternal serum DDE level (85) and reinforcing the concept that DDT has adverse effects on reproductive outcome if the offspring is exposed to DDT *in utero*. Gerhard et al. (86) had suggested earlier that chlorinated hydrocarbons may play a role in female infertility and also underly certain gynecological conditions.

Currently available data, mainly on animals, suggest that exposure to persistent chemicals particularly during critical periods of development may involve elevated risk of reproductive dysfunction, indicating the need for further investigations. Recent research has shown a number of pesticides and some of their metabolites to have estrogenic activity disruptive to normal hormone action (87). Endocrine disruptive effects of endosulphan evaluated by the sexual maturity rate (SMR) and hormone levels in school children in India has been reported (88). On the basis of adverse health effects of some pesticides observed in workers, it is necessary to promote integrated pest management and to find out ecologically sound alternates for pesticides as well as providing education about the safe handling of these chemicals.

Solvent exposure and reproductive toxicity

Exposure to solvents can occur occupationally as in manufacturing processes, dry-cleaning, degreasing, painting and paint removal, printing. Solvents are volatile and lipophilic in nature and workers may be exposed through inhalation or the dermal route. In view of their lipid solubility, it is likely that most organic solvents traverse the placenta and reach into the foetus. In humans, occupational exposure to organic solvents has been related to disorders of reproductive health like menstrual disorders, reduced fertility and adverse pregnancy outcomes. A retrospective cohort study among the workers of semiconductor manufacturing plants in USA has shown that exposure by female staff to mixtures containing ethylene glycol ether was associated with increased risk of spontaneous abortion and sub-fertility. However, among spouses of the male staffs there was no increased risk of spontaneous abortion from potential exposure to mixtures containing ethylene glycol ether, but there was a non-significantly increased risk of sub-fertility (89). In shipyard painters exposed to 2-ethoxy ethanol (2-EE), an increased odds ratio for a lower total sperm count was found relative to the non exposed workers at the same shipyard, without a concurrent change in serum LH, FSH or testosterone concentration (90). Long-term exposure to ethylene dibromide (EDB) resulted in decline of sperm motility and viability, suggesting that the short-term exposure may slow sperm velocity, but longer exposures may cause immotility and cell death. Moreover, the accessory sex glands may be affected by exposure to EDB (91).

Significantly higher frequency of asthenospermia, hypospermia and teratospermia as compared to the controls was reported in factory workers exposed to carbon disulphide (CS_2) (92). The ratios of the number of miscarriages against the number of living children in the families of workers exposed to CS_2 correlated well with the environmental concentration of CS_2 (93). Vanhoorne et al. reported that CS_2 significantly reduced male libido and potency, without similar effects on fertility and semen quality (94). Similarly, Meyer had found no significant difference in sperm count, ejaculated volume and morphology pattern between the CS_2 exposed and unexposed groups (95). Pieleszek studied the effect of CS_2 on menopause, concentration of monoamines, gonadotropins, estrogens and androgens in women exposed chronically to CS_2 in concentrations of 9.36-23.4 mg/m^3. Menopause was present in 16.59% of the study population as compared with 8.05% in the normal population. Mean age at menopause and serum concentrations of estrone, estradiol, progesterone, 17-hydroxyprogesterone were significantly lower in women chronically exposed to CS_2. However, no significant differences in the level of FSH or LH were noted between the exposed and control groups (96). There have been earlier reports of increased incidence of spontaneous abortion due to exposure to CS_2 (97,98). However, a community based study of spontaneous abortion, occupation, and air pollution carried out by Hemminki and Niemi found no relationship between CS_2 concentration and miscarriage rates (99). Hence, most of the available data provide some indication that CS_2 may affect the reproductive system of both sexes.

Kolastad et al. observed a statistically significant decline in sperm density from 63.5 to 46.0 million sperm/ml during exposure to styrene, where as no decline was seen in the non-exposed subjects (100). Styrene has been shown to cross human placenta. Although some epidemiological studies suggest that exposure to styrene involves reproductive hazards, the validity of most of the studies is weakened by methodological shortcomings and thereby no firm conclusion can be drawn (101). Investigation of the relationship of birth weight with maternal and paternal exposure to organic solvents in 1222 couples employed in a petrochemical corporation in China has shown a significant correlation between maternal, but not paternal, exposure to solvents and the outcome of reduced birth weights (102). Exposure of women workers to petrochemicals including benzene, gasoline and hydrogen

sulphides increased the risk of spontaneous abortion (103). Working within dry cleaning units utilising perchloroethylene, a higher risk among operators as compared to those not employed either dry cleaning or laundry units during pregnancy, increased the risk of spontaneous abortion (104). A significantly greater incidence (3.6 times, $p<0.05$) of spontaneous abortion during the first 3 months of pregnancy as compared to the unexposed women was also reported (105). The results of case-control studies within two cohorts of women engaged in laundry or dry-cleaning work in Sweden validate the recommendation that tetrachloroethylene should be handled with caution by women in childbearing ages (106). Other epidemiological studies together with evidence from animal studies suggest that exposure to perchloroethylene may be a risk factor for spontaneous abortions.

The solvent 2-bromopropane (2-BP) has also been implicated for toxicity in the reproductive system in both human and experimental studies. Mass intoxication of workers at an electronic company in Korea resulted in 17 out of 25 female workers in ovary dysfunction accompanying amenorrhea. Six out of eight male workers showed oligospermia or azoospermia. The report of the advent further indicated that 2-BP might be toxic to the haematopoietic as well as the reproductive system (107). Dysmenorrhoea seemed to occur more often in the female workers highly exposed to toluene (range 50-150 ppm; mean 88 ppm) when compared either to other workers in the same factory who had little or no exposure to toluene (0-25 ppm) or another control group of working women from the outside community. It was concluded, however, that it is uncertain whether dysmenorrhoea was associated specifically with exposure to toluene, since other behavioral and work-related factors could have also resulted in dysmenorrhoea (108). Low daily exposure to toluene in women seemed to be associated with reduced fecundity (109). These results suggest that organic solvents in general may adversely influence both the male and female reproductive systems.

Other occupational/environmental situations and reproductive impairments

An epidemiological study among male workers of a rubber factory indicated a significant increase in the frequency of abortions and congenital malformations in the family of exposed workers. It was suggested that undue exposure of men to rubber chemicals resulted in genetic damage (110). Damage to the spermatogenic process resulting from exposure to hydrocarbons in the rubber industry was revealed by an increased rate of abnormalities in the semen of exposed workers (111). Recently Zaidi et al. reported that spray painters exposed to volatile organic solvents, resins monomers, and pigments (heavy metals) are at risk of developing neurological, thyroid and reproductive problems (112). Adverse effects of the welding profession on the motility, morphology and physiological functions of human sperm has also been suggested (113).

The phthalate group of compounds, which are the most abundant man-made chemicals in the environment, might have adverse effects on reproduction. Analysis the data with respect to the concentration of di-butylphathalate in the cellular fraction of ejaculates and sperm density or the total number of sperms has indicated a negative correlation between phthalate concentration and sperm production (114). There is recent evidence for a dose-response relation between monobutyl phthalate and monobenzyl phthalate and adverse effects on one or more of the parameters of semen quality, i.e., sperm concentration, motility and morphology, plus suggestive evidence a for similar relationship between monomethyl phathalate and sperm morphology (115).

Dioxin, an industrial byproduct, is considered one of the most toxic man made substances. Research has linked high serum concentrations of dioxin in the parents with relative increase in the number of female births as compared to male births i.e., 'lowered sex ratio' after exposure to dioxin (116); and appears to persist for years after exposure. It was mentioned that the average concentration of dioxin in fathers was similar to the doses that induced reproductive impairments in rats, and about 20 times the estimate average concentration of dioxin currently found in human beings in industrialized countries (117). The sex ratio of the children born to workers exposed to high levels of dioxin during the production of the biocide trichlorophenol and the herbicide 2,4,5-trichlorophenoxy acetic acid was associated with the birth of more girls, but only for paternal exposures (118). On the other hand, exposure of fathers to polychlorinated biphenyls (PCBs) was linked to a higher population of male offsprings (119). Examination of the wives of workers exposed to 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) and wives of non-exposed neighborhood referents showed no association between paternal TCDD level at the time of conception and spontaneous abortion among pregnancies fathered by workers with TCDD levels of <20 to 1,120 ppt as compared to pregnancies fathered by referents. The sex ratio [males/(males+females)] of offspring also did not differ by exposure to TCDD (120). Rier et al. conducted a long-term study on the health effects of chronic exposure to dioxin (25 ppt and 5 ppt dioxin in feed) in rhesus monkeys for a period of 4 year. Examination of the animals ten years after terminating the dioxin treatment showed that chronic exposure to dioxin was directly correlated with a significant increased incidence in the development of endometriosis (121). This study is of concern because endometriosis was observed at very low chronic doses of dioxin.

Data available on the association of exposure to chemicals and adverse reproductive outcome in humans are equivocal due to lack of exposure parameters and appropriate study design. The exact role of male mediated toxicity on such adverse effects like abortions, congenital malformations, pre-term delivery etc. is not yet fully understood. The available data on various endocrine disrupters and risk factors (malnutrition and infections which can exaggerates the risk) suggest a greater vulnerability of the population of developing or underdeveloped countries to reproductive hazards from exposure to these chemicals. Thus there is a need to constantly monitor both exposure and affect parameters such as congenital malformations, subnormal growth and development, testicular cancer, hypospadias, cryptorchidism,

breast cancer etc. and trend of semen quality in a given population and ethnic groups. The data are inadequate and need confirmation. It is necessary to review the indiscriminate use of synthetic chemicals with hormone-like effects. Further, the general public needs to be educated for vigilant use of these chemicals. The risk assessment to the human is absolutely necessary for the chemicals that have already proven to be toxic to the reproductive system in animal studies.

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