

## Review

# Occupational Exposure Associated with Reproductive Dysfunction

Sunil KUMAR

Reproductive Toxicology and Histochemistry Division, National Institute of Occupational Health, India

**Abstract: Occupational Exposure Associated with Reproductive Dysfunction: Sunil KUMAR. Reproductive Toxicology and Histochemistry Division, National Institute of Occupational Health, India**—Evidence suggestive of harmful effects of occupational exposure on the reproductive system and related outcomes has gradually accumulated in recent decades, and is further compounded by persistent environmental endocrine disruptive chemicals. These chemicals have been found to interfere with the function of the endocrine system, which is responsible for growth, sexual development and many other essential physiological functions. A number of occupations are being reported to be associated with reproductive dysfunction in males as well as in females. Generally, occupations involving the manufacture/or application of some of the persistent chemicals that are not easily degradable as well as bio-accumulative chemicals, occupations involving intensive exposure to heat and radiation, occupations involving the use of toxic solvents as well as toxic fumes are reported to be associated with reproductive dysfunction. Occupational exposure of males to various persistent chemicals have been reported to have male mediated adverse reproductive outcomes in the form of abortion, reduction in fertility etc. with inconclusive or limited evidence. Nevertheless, there is a need for more well designed studies in order to implicate any individual chemical having such effects as in most occupations workers are exposed to raw, intermediate and finished products and there are also several confounding factors associated with lifestyles responsible for reproductive dysfunction. There is an urgent need to look at indiscriminate use of persistent chemicals especially pesticides and persistent organic pollutants (POP's) as these chemicals enter the food chain also and could be potential for exposure during the critical period of development. It is also necessary to impart information, and to educate about the safe use of these chemicals,

as a very sensitive reproduction issue is involved with exposure to these chemicals. Occupational exposures often are higher than environmental exposures, so that epidemiological studies should be conducted on these chemicals, on a priority basis, which are reported to have adverse effects on reproduction in the experimental system.

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Human beings are exposed to several thousand exogenous chemicals used in industrial processes, developmental activities and also through the food chain. Disorders of reproduction and hazards to reproductive health and associated functions have become prominent issues in recent decades after reports of adverse effects of certain chemicals on reproductive function. The male reproductive system is vulnerable to the effects of the chemicals and physical factors. This might be because sensitive events take place during spermatogenesis and the persistent environmental pollutants and/or physical factors may affect some of these events to some extent. The female reproductive system is also vulnerable to persistent chemicals or pollutants 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. Nevertheless, women's health is also an area that is gaining attention with the realization that men's and women's bodies react differently to environmental agents<sup>1)</sup>. 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. Disruption of ovarian function greatly affects women's reproductive and endocrine health. Certain environmental factors may affect the female endocrine system and thus play an important role

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Correspondence to: S. Kumar, Reproductive Toxicology and Histochemistry Division, National Institute of Occupational Health, Meghani Nagar, Ahmedabad-380016, India  
(e-mail: sunilnioh@yahoo.com)

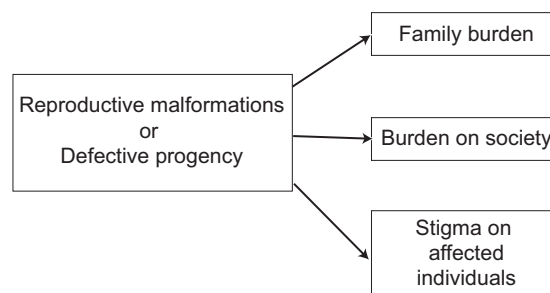
in the increasing infertility problem.

Sometimes, people are exposed to various risk factors for reproduction such as toxic chemicals, radiation, intense heat, etc. in their workplace without knowing their exposure. Occupational exposure to these factors are generally higher than environmental exposure. However, in most cases, people are not aware of the hazard on reproduction due to these occupational exposures until they are interested in childbirth. The problem of infertility has increased from 8 to 15% over the past two decades in industrialized countries<sup>2,3</sup>. Workplace exposure offers the best opportunities for studying the effects of reproductive toxicants and it is more feasible to design and conduct valid studies in the workplaces in spite of problems related to participation of the workers and their employers. Further, data on occupational exposure can be extrapolated to the general population exposed to environmental pollutants.

Reproductive organ malformations and defects in progeny have enormous emotional and practical implications for not only the affected person but also for their family as well as to society (Fig. 1). Therefore we must ensure that genetic material is passed unaffected to progeny. In the present paper the author has tried to provide a comprehensive summary of occupational exposure and associated reproductive hazards. The literature was collected by searching various databases such as Pub Med, Medline and certain other websites as well as consulting various journals especially on occupational health. The paper is divided into several heads based on the type of occupational exposure and associated reproductive outcome. This review is mainly based on the data available on human male and female reproductive dysfunction, but some references related to animal experiments has also been incorporated whenever necessary in the absence of or scanty data on humans. Earlier published reviews generally deal with either male or female reproduction. The present review reports recent trends in reproductive dysfunction in both sexes and also incorporates an emerging area of environmental endocrine disruptors and reproductive health. The results based on various studies related to male and female human reproduction are summarized in Tables 1–6.

### Occupations involving pesticide exposure

Pesticide factory workers and/or applicators engaged in the manufacture, formulation and application of pesticides are exposed to these chemicals through different routes while handling or spraying. The general population is also exposed to these pesticides or their metabolites to some extent, even through the food chain, as some of the pesticides persist in the environment and are also bio-accumulative. It is rational to believe that pesticides, which are toxic to pests, might produce some adverse health effects including reproductive effects on



**Fig. 1.** Stigma/burden associated with reproductive dysfunction

living beings including humans. The United Nations Environment Protection (UNEP) reported that nine of the twelve most unwanted persistent organic pollutants (POPs) are pesticides used on agriculture crops and for public health vector control programmes. These twelve POPs have been identified by the UNEP organization as a powerful threat to human and wildlife health on a global basis<sup>4</sup>.

Human exposure to pesticides may occur by virtue of occupation or environment. A classical example of reproductive toxicant is 1,2-dibromo-3-chloropropane (DBCP), which was in use since the mid-1950. Its spermatotoxic effects in rats were discovered in the earlier 60s, but its deleterious effects on human spermatogenesis were discovered only in 1977. It was noted that there was paucity of children among the workers in a DBCP plant in California, after they had started to work in DBCP production<sup>5</sup>. They further reported that occupational exposure to DBCP caused a reduction in the sperm concentration in ejaculates from a median of 79 million cells/ml in unexposed men to 46 million cells/ml in exposed workers<sup>6</sup>. A study on six workers exposed to DBCP in a pesticide factory in Israel who underwent testicular biopsy reported complete atrophy of the seminiferous epithelium<sup>7</sup>. This suggests that DBCP is a powerful male reproductive toxicant and might be directly affecting testicular tissues and spermatogenesis. Multigner and Spira<sup>8</sup> reported results of studies undertaken in factory workers in Mexico and field workers in Hawaii and Costa Rica among DBCP exposed workers, and found similar results on testicular dysfunction. Mattison *et al.*<sup>9</sup> studied the hormone level and semen of male workers involved in the manufacture of DBCP and reported a high level of LH and FSH in serum and a reduced sperm count in these workers. They have also suggested that these effects are apparently related to DBCP action on the Leydig cells to alter androgen production and action. On the basis of available data on DBCP one can conclude that DBCP is a potent male reproductive toxicant affecting both reproductive and endocrine function.

In addition to DBCP, there is some evidence of reproductive toxicity of a few other pesticides such as carbaryl and 2,4-dichloro phenoxy acetic acid, etc. Wyrobek *et al.*<sup>10</sup> reported harmful effects of carbamate pesticide (carbaryl) on sperm morphology. A significantly higher level of asthenozoospermia and teratozoospermia were found in 2,4-D (2,4-dichloro phenoxy acetic acid) exposed workers engaged in spraying as compared to unexposed control subjects<sup>11</sup>. A few studies are also available on the effects of multiple pesticides exposure on the reproductive system of male workers, which may affect the reproductive outcome. A study conducted by Rupa *et al.*<sup>12</sup> from India among male workers who were exposed to various pesticides such as DDT, BHC, endosulfan; and organophosphorus pesticides i.e. malathion, methyl-parathion, dimethote, monocrotophos, phosphamidon and quinalphos; synthetic pyrethroids such as fenvelrate and cypermethrin during mixing and spraying showed male mediated adverse reproductive outcome such as abortion, stillbirths, neonatal deaths, congenital defects, etc. Nevertheless, it is not possible to pinpoint any particular pesticide on the basis of these results, as these are the cumulative effects of a number of pesticides. Furthermore, Abell *et al.*<sup>13</sup> studied the testicular function of greenhouse workers exposed to pesticides and reported that male fecundity may be at risk from exposure to pesticides in the manual handling of cultures in green houses. A significantly increased risk of cryptorchidism i.e. undescended testicles was found in sons of women working in gardening as observed by Weidner *et al.*<sup>14</sup>. They reported that this increased risk of cryptorchidism among sons of female gardeners could suggest an association with prenatal exposure to occupationally related chemicals having estrogenic and other hormone-disruptive effects.

Some epidemiological studies of agricultural workers, chemical industry workers and other exposed individuals have shown a positive association with pesticide exposure and reduced fertility among men and women, as well as spontaneous abortion, birth defects and other pregnancy outcomes<sup>12, 15–17</sup>. A study carried out in India by Rita *et al.*<sup>16</sup> among workers occupationally exposed to pesticides in the grape gardens of Andhra Pradesh also indicated a high percentage of abortions (43.75%) in exposed workers as compared to 7.5% in the control subjects. Spontaneous abortion has also been related to maternal pesticide exposure in indoor gardening as reported by Heidam<sup>17</sup>. A study carried out in China indicated that 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<sup>18</sup>. Nurminen<sup>19</sup> reviewed the published work on maternal pesticide exposure and pregnancy outcome and concluded that published studies have given some indications of increased reproductive risk and exposure to pesticides

but the epidemiological evidence does not allow any clear inference to be drawn. The present available data mainly on animals suggest that exposure to persistent organochlorine chemicals particularly during the critical period of development might have increased risk of reproductive dysfunction, but more data on occupational exposure to pesticide and reproductive outcome are required to correlate them with the residue levels.

Higher levels of organochlorine compounds and PCBs have been found in women with miscarriages than in women with a normal course of pregnancy<sup>20, 21</sup>. Nevertheless, Gerhard *et al.*<sup>22</sup> reported that chlorinated hydrocarbon levels were similar in women with primary or secondary and early or late miscarriages, neither was there a difference between women with hormonal or immunological disorders as causes of repeated miscarriages and women with idiopathic repeated miscarriages. But significant associations were found between an increasing level of chlorinated hydrocarbons in blood and immunological and hormonal changes, so that chlorinated hydrocarbons might have an impact on the pregnancy course in certain cases. Eckrich and Gerhard<sup>23</sup> noted that women with repeated miscarriages had a higher level of certain chlorinated hydrocarbons than in the total population, which was investigated in a group of more than 1900 women of the same region. In 20% of the women with repeated miscarriages, at least one of the chlorinated hydrocarbon levels was found to be above the reference range. Recently, Longnecker *et al.*<sup>24</sup> provided some evidence about the adverse effects of DDT, a chlorinated hydrocarbon, in humans. They have shown a powerful association between DDE levels in mother's blood and the likelihood of pre-term birth. In data from the 1960s in the United States, they found that the higher the level of DDE, the more likely the birth would be pre-term. They also reported that contamination was linked to the baby's size, with babies more likely to be small for their gestational age when born to mothers with higher DDE levels. A case control study carried out by Korrick *et al.*<sup>25</sup> reported a relationship between risk of spontaneous abortion and DDE concentration in maternal serum. These findings reinforce the concept that DDT might have adverse effects on reproductive outcome if offspring are exposed to DDT *in utero*. Later, Gerhard *et al.*<sup>26</sup> suggested that chlorinated hydrocarbons may play a role in female infertility and may be an underlying factor in certain gynecological conditions. Furthermore, Gerhard *et al.* had shown concerning pentachlorophenol (PCP), which is an anti-microbial agent, used worldwide in industry, agriculture and households as a constituent of wood preservatives, significant associations between the serum PCP concentration and impairment of different parameters of the endocrine system<sup>27</sup>. They suggested that PCP might act centrally at a hypothalamic or suprahypothalamic

**Table 1.** Reproductive dysfunction due to pesticide exposure

| Names of the pesticides  |   | Observed effects  | References   |
|--------------------------|---|---|--|
| Male Reproductive System |   |   |  |
| 1                        | di-bromochloropropane (DBCP)                                    | Reduction in sperm concentration, and infertility<br>Atrophy of the seminiferous epithelium<br>Testicular dysfunction<br>High level of serum LH and FSH and reduced sperm count | Whorton <i>et al.</i> <sup>5, 6)</sup><br>Potashnik <i>et al.</i> <sup>7)</sup><br>Multigner and Spira <sup>8)</sup><br>Mattison <i>et al.</i> <sup>9)</sup> |
| 2                        | Carbaryl  | Deterioration of sperm morphology   | Wyrobek <i>et al.</i> <sup>10)</sup>   |
| 3                        | 2,4-dichloro phenoxy acetic acid (2-4 D)                        | Asthenozoospermia and teratozoospermia  | Lerda and Rizzi <sup>11)</sup>   |
| 4                        | Multiple pesticide exposure among cotton growers                | Male mediated adverse reproductive performance  | Rupa <i>et al.</i> <sup>12)</sup>  |
| 5                        | Multiple pesticide exposure among greenhouse workers            | Reduced sperm concentration and testosterone level  | Abell <i>et al.</i> <sup>13)</sup>   |
| Female                   |   |   |  |
| 1                        | Multiple chemical /pesticide exposure in female gardeners       | Casual association of cryptorchidism with occupation among sons of female gardeners   | Weidner <i>et al.</i> <sup>14)</sup>   |
| 2                        | Multiple pesticide exposure in grape garden workers             | Higher abortion rates   | Rita <i>et al.</i> <sup>16)</sup>  |
| 3                        | Women exposed to pesticides during first trimester of pregnancy | Small for gestational age   | Zhang <i>et al.</i> <sup>18)</sup>   |
| 4                        | Maternal pesticide exposure in indoor gardening                 | Spontaneous abortion  | Heidam <sup>17)</sup>  |
| 5                        | Maternal serum DDE level  | Increased risk of spontaneous abortion  | Korrick <i>et al.</i> <sup>25)</sup>   |
| 6                        | Maternal serum DDE level  | Increased risk of pre-term delivery   | Longnecker <i>et al.</i> <sup>24)</sup>  |

level, and may result in mild ovarian and adrenal insufficiency. PCP may, therefore, play a role in the increasing infertility problem. The data on pesticide exposure and reproductive impairment is summarized in Table 1.

Recent studies have indicated a new form of reproductive effect through an endocrine disruptive mechanism and a number of pesticides and some of their metabolites have been reported to have estrogenic activity, affecting normal hormone function<sup>28, 29)</sup>. In view of adverse health effects observed to some extent in workers/applicators with some pesticides, it is necessary to promote integrated pest management and to find out ecologically sound alternatives to pesticides and also to impart education to the workers and farmers about the safe use of these chemicals in order to reduce reproductive health risk associated with exposure.

### Occupations involving toxic metal exposure

Workers are exposed to various toxic metals and their oxides in a number of occupations. Detailed studies on human reproduction with reference to heavy metals are scanty, but lead is an exception. The effect of various heavy metals such as mercury, lead, cadmium and chromium, etc. on male and female reproduction has been

studied in detail in experiments. A number of epidemiological studies indicated that occupational exposure to lead has adverse effects on human sperm. A study on workers at a newspaper printing press in Ahmedabad, India conducted by this laboratory indicated that the average sperm counts were significantly lower and a lesser proportion of them were found to be motile in exposed subjects as compared to controls. These changes were associated with the level of lead in the blood of the workers<sup>30)</sup>. Matthies *et al.*<sup>31)</sup> reported dose dependent blood lead level and a reduction in the fertility index among lead-exposed workers. Recently, Apostoll *et al.*<sup>32)</sup> reviewed the literature on male reproductive toxicity of lead in animals and humans. They reported that human studies focused mainly on semen quality, endocrine function, and birth rates in occupationally exposed subjects. These human studies showed that exposure to inorganic lead greater than 40 µg/dl in blood impaired male reproductive function by reducing sperm count, volume and density, or changing sperm motility and morphology, but no relevant effects were detected on the endocrine profile. Furthermore, on the basis of a cross sectional study among men employed at a lead smelter unit, Alexander *et al.*<sup>33)</sup> concluded that blood lead concentrations below the currently accepted worker

protection criteria seem to adversely affect spermatogenesis. Very recently, Bonde *et al.*<sup>34)</sup> reported that adverse effects of lead on the sperm concentration and susceptibility to acid induced denaturation of sperm chromatin are unlikely at blood lead concentrations below 45 µg/dl, but effects of low-level exposure to lead on the other measures of testicular function cannot be ruled out. This study confirmed the conclusion of Apostoll *et al.*<sup>32)</sup> about the doses of lead which can cause reproductive dysfunction.

Daniell<sup>35)</sup> reported that painters and construction workers supposed to be exposed to lead and solvent during occupation also have adverse effects on both male and female reproduction. Mehta and Anandkumar<sup>36)</sup> reported a decline in the sperm count in a study of population from Bangalore, India and they have correlated this decline with the changes in various pollution indices such as suspended particulate matter, sulphur dioxide and lead. Recently Dawson *et al.*<sup>37)</sup> compared the sperm viability with metal levels in seminal plasma among sixty-four apparently healthy men. Significant differences were observed between the high and low live sperm groups for Pb ( $p < 0.01$ ) and Al (0.05) but not for Cd. Furthermore, 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 the metal level. This study suggests that the presence of these metals in the environment of workers may affect normal spermatogenesis. Recently, Telisman *et al.*<sup>38)</sup> 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. All the available studies clearly suggest that lead exposure close to a dose of 40 µg/dl might have adverse effects on spermatogenesis and male reproductive endocrine function. Lin *et al.*<sup>39)</sup> studied paternal occupational lead exposure and low birth weight/pre-maturity, and reported that there were no significant differences in birth weight or gestational age between the exposed and control groups, but workers with high blood lead levels for more than 5 yr had a higher risk of fathering a child of low birth weight or prematurity than did controls.

Mercury is also known to have deleterious effects on the male reproductive system with limited evidence. Occupational alkyl mercury exposure has been reported to cause reduced sperm counts and terato and asthenozoospermia<sup>40)</sup>. In another study, twenty-two men occupationally exposed to mercury were reported to have impairment of the fertility index and their concentration of seminal mercury was ten times higher than the serum concentration<sup>31)</sup>. These findings indicate that mercury may accumulate in the testicular or epididymal tissues and may be responsible for a higher concentration in the semen. An earlier animal study carried out in this

laboratory indicated localization of mercury in the interstitial region as well as cytoplasmic and nuclear components of Leydig cells<sup>41)</sup>. Recently, Schuurs<sup>42)</sup> reviewed the work on occupational mercury exposure and reproductive toxicity. He mentioned that it seems warranted to conclude the negative reproductive effects from exposure to mercury in the dental office are unproven but safe levels have not been established. He further suggested that more research is needed concerning the effects of occupational elemental mercury concentrations lower than the TLV on the menstrual cycle, conception, male fertility and children's behavior.

Another metal, which may have implications for reproductive dysfunction, is chromium as a number of reports are available on changes in reproductive function in the experimental system<sup>43, 44)</sup>. A recent report of Li *et al.*<sup>45)</sup> also suggested that occupational exposure to chromium may lead to changes in semen quality and the reproductive hormone level. A recent study carried out at our laboratory on chromium-exposed workers in a chemical industry revealed non-significant changes in the sperm concentration, motility, and viability as compared to the controls, but abnormality in sperm morphology was higher in chromium-exposed workers than in controls (unpublished data). Welders comprise a major occupational group with known exposure to toxic fumes containing certain metals and their oxides, gases and intense heat, etc. during welding, so that they are exposed to toxic chemicals and a physical environment. Bonde<sup>46)</sup> has reported that the sperm count per ejaculate, the proportion of normal sperm count, the degree of sperm motility and the linear penetration rate of the sperm were moderately decreased. He also observed a dose-response relationship between total exposure to welding fumes and these sperm parameters (except sperm count). In addition, Bonde *et al.*<sup>47)</sup> also reported a reduction in fertility among welders associated with the welding of mild steel, but not with the welding of stainless steel. Furthermore, he studied semen quality in welders exposed to radiant heat and suggested a reversible decrease in semen quality, most likely caused by moderate exposure to radiant heat<sup>48)</sup>. Earlier, he also studied semen quality in welders before and after three weeks of non-exposure and reported no consistent improvement in any semen parameter in the follow-up period relative to the pre-exposure period in either mild steel or stainless steel welders<sup>49)</sup>. Furthermore, a recent study in welders carried out at the author's laboratory indicated that the welding profession may not have considerable effects on the sperm concentration but may affect the motility, morphology and physiological function of the sperm even though the sample size was small, but hormonal changes did not show any definite pattern and need detailed study<sup>50)</sup>. Bonde and Ernst<sup>51)</sup> studied the level of sex hormones and semen quality in welders exposed to hexavalent chromium and reported

**Table 2.** Reproductive dysfunction due to metal exposure

| Name of the metal          |                                 | Observed effects   | References   |
|----------------------------|---------------------------------|--|--|
| Male Reproductive System   |                                 |  |  |
| 1                          | Lead                            | Lower sperm count and motility   | Roy Chowdhury <i>et al.</i> <sup>30)</sup>   |
|                            |                                 | Reduction in fertility   | Matthies <i>et al.</i> <sup>31)</sup>  |
|                            |                                 | Impaired reproductive function by reducing sperm count, motility, morphology | Apostoll <i>et al.</i> <sup>32)</sup>  |
|                            |                                 | Adverse effects on sperm   | Bonde <i>et al.</i> <sup>34)</sup>   |
|                            |                                 | Spermatogenesis impairment   | Alexander <i>et al.</i> <sup>33)</sup>   |
|                            |                                 | Reduced semen quality  | Telisman <i>et al.</i> <sup>38)</sup>  |
| 2                          | Mercury                         | Reduction in sperm count and terato and asthenozoospermia                    | Popschu <sup>40)</sup>   |
|                            |                                 | Impairment of fertility index  | Matthies <i>et al.</i> <sup>31)</sup>  |
| 3                          | Chromium                        | Changes in semen quality and reproductive hormones                           | Li <i>et al.</i> <sup>45)</sup>  |
|                            |                                 | Deterioration in sperm morphology  | (unpublished)  |
| 4                          | Lead Cadmium and Aluminum       | Deterioration in motility  | Dawson <i>et al.</i> <sup>37)</sup>  |
| Female Reproductive System |                                 |  |  |
| 1                          | Mercury                         | Stored in pituitary gland and affects the production of gonadotropins        | Danscher <i>et al.</i> <sup>57)</sup>  |
| 2                          | Lead                            | Increased risk of low birth weight and neural tube defects                   | Irgens <i>et al.</i> <sup>53)</sup>  |
| 3                          | Increased heavy metal body load | Greater risk of miscarriages, foetal malformations, premature births         | McMichael <i>et al.</i> <sup>54)</sup><br>Laudanski <i>et al.</i> <sup>55)</sup> and Fagher <sup>56)</sup> |

that low level exposure to hexavalent chromium associated with tungsten inert gas stainless steel and mild steel welding do not appear to be a major hazard for human spermatogenesis. In addition, Jernes and Knudsen<sup>52)</sup> also reported no difference between welders and non-welders in semen quality. Therefore, data available on reproductive impairments due to welding exposure are inconclusive and need further study.

Effects of heavy metals on the human female reproductive system are too scanty to reach any firm conclusion, but a considerable number of experimental studies are available regarding the effect of heavy metals on the structure and function of the ovary including foetal development. Irgens *et al.*<sup>53)</sup> studied the associations between occupational lead exposure and reproductive outcome. They observed that offspring of lead-exposed mothers had an increased risk of low birth weight and neural tube defects, but offsprings of lead exposed fathers had no increased risk in any of the analysed reproductive outcomes of that study<sup>53)</sup>. A number of investigators suggested that pregnancies that occur despite an increased heavy metal body load are at greater risk of miscarriage, foetal malformation, placental insufficiency and premature birth<sup>54–56)</sup>. Danscher *et al.*<sup>57)</sup> 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. Gerhard *et al.*<sup>58)</sup> suggested that 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. Furthermore, various *in vitro* and *in vivo* studies reported that in the ovary itself, accumulation of heavy metals impairs the production of estradiol and progesterone<sup>59–60)</sup>. These hormonal changes might affect female fertility. Recently, Gerhard *et al.*<sup>61)</sup> suggested that heavy metal induced hormonal and immunological changes might be important factors in the pathogenesis of repeated miscarriages. All these studies suggest that heavy metals might have effects on the female reproductive system affecting the ovary as well as hormonal production and release. The data on metal exposure and reproductive dysfunction are summarized in Table 2.

### Occupation associated with radiation induced reproductive dysfunction

Workers are exposed to higher doses of ionizing radiation accidentally as well as during their occupation as compared to environmental radiation exposure. Sometimes industrial workers have to do repair work after the accidental spillage of radioactive material, which leads to exposure to very high doses of unwanted radiation. All living organisms are also exposed to some amount of

**Table 3.** Reproductive dysfunction due to radiation exposure

| Type of exposure/ groups  | Observed effects  | References                                |
|---|---|---|
| <b>Male Reproductive System</b>   |   |   |
| 1 Doses 0.1 to 0.15 Gy  | Temporary sterility   | UNSCEAR <sup>67)</sup>                    |
| 2Gy and possibly about 6 Gy   | Permanent aspermia  | UNSCEAR <sup>67)</sup>                    |
| 0.11 Gy testicles X-irradiation   | Suppression of sperm count  | Clifton and Bremner <sup>68)</sup>        |
| 3–5 Gy testicles X-irradiation  | Permanent sterility   | Clifton and Bremner <sup>68)</sup>        |
| 1.4 to 6 Gy gamma rays  | Reduction in sperm count  | Kumatori <i>et al.</i> <sup>69)</sup>     |
| Cleaners of Chernobyl sites   | Disorders of spermatogenesis  | Cheburakov and Cheburakova <sup>70)</sup> |
| 2 High frequency electromagnetic radiation (Radar operator)             | Reduction in sperm count  | Weyandt <i>et al.</i> <sup>71)</sup>      |
| 3 Microwaves  | Reduction of sperm concentration, motility and normal sperm morphology  | Lancranjan <i>et al.</i> <sup>72)</sup>   |
| <b>Female Reproductive System</b>                                       |   |   |
| 1 Doses 1.7 to 6.4 Gy   | Temporary sterility   | UNSCEAR <sup>67)</sup>                    |
| 3.3 to 10 Gy  | Permanent sterility   |   |
| 2 Internal alpha particle radiation dose of more than 5 Sv to the ovary | Declines in number of pregnancies and live births   | Schieve <i>et al.</i> <sup>73)</sup>      |
| 3 Exposure to electric and magnetic fields                              | Evidence is lacking for a close association between women working in front of video display terminals and foetal loss and adverse pregnancy outcome | Shaw <sup>74)</sup>                       |

radiation coming from outer space or emitted from the radioactive isotopes present in the environment. The effects of radiation on reproduction have been known since the 1920s. Radiation exposure of mother, father or a developing foetus can cause adverse reproductive effects<sup>62)</sup>. A large number of experimental data are available on the adverse effects of radiation on the male and female reproductive systems of various animal species<sup>63–66)</sup>. Saharan and Uma Devi<sup>65)</sup> studied the effects of whole body gamma radiation on the testicular tissue of mice and reported that both testis weight and the total germ cell population showed a drastic reduction in the irradiated groups as compared to the controls. Vergouwen *et al.*<sup>66)</sup> studied the effects of pre-natal irradiation on post-natal development of mouse testis and reported that spermatogonial stem cells of foetal testis are more sensitive to X-irradiation than the testis of adult mouse, whereas Sertoli cells and interstitial cells are relatively resistant. Limited reproductive data on human beings with radiation exposure are also available. The reproductive systems of both males and females are sensitive to radiation. Irradiation of the testes produces sterility, which may be permanent or temporary depending on the dose levels as well as the dose rate employed. Doses as low as 0.1 to 0.15 Gy have been reported to cause temporary sterility, although >2 Gy and possibly about 6 Gy are needed to produce permanent aspermia<sup>67)</sup>.

A study carried out in the United States among more than 100 prisoners, who volunteered themselves for testicle X-irradiation showed that a dose of 0.11 Gy can causes substantial suppression of sperm counts and a dose of 3 to 5 Gy could lead to permanent sterility<sup>68)</sup>. Multigner and Spira<sup>8)</sup> suggested that after a radiation dose of between 2 and 3 Gy, the primary site of damage is the germinal epithelium, with recovery of spermatogenesis sometimes delayed for up to 10 yr or more. An earlier study in which Japanese fishermen were exposed to fallout doses of gamma rays estimated at about 1.4 to 6 Gy over 14 d, corresponding to approximately 0.7 to 3 Gy given as a single dose indicated that sperm counts of these fishermen were severely depressed, but began to increase two years after exposure and most of these men produced healthy children<sup>69)</sup>. A study on semen quality of cleaners at the Chernobyl sites in Russia showed disorders of spermatogenesis in exposed men. The most severe changes in the majority of the cases were in the form of asthenooligospermia. These changes were noticed in men exposed to a dose higher than 100 m Sv<sup>70)</sup>. Wayandt *et al.*<sup>71)</sup> reported preliminary data on semen analysis of radar operators and reported a reduction in the sperm count of military radar operators exposed to high frequency electromagnetic radiation. Earlier, Lancranjan *et al.*<sup>72)</sup> conducted a study among technicians exposed to microwaves for a period of 1 to 17 yr and reported a

**Table 4.** Reproductive dysfunction due to exposure to high temperature

| Temperature/workers involved   | Observed effects                     | References                                 |
|--|--------------------------------------|--|
| Male   |                                      |  |
| 1 Workers exposed to high temperature in the ceramic industry  | Increased sperm abnormality          | Figa-Talmanca <i>et al.</i> <sup>76)</sup> |
| 2 Metal alloy steel welders with moderate exposure to radiant heat but without substantial exposure to welding fumes | Reversible decrease in semen quality | Bonde <sup>48)</sup>                       |

significant decrease in the sperm concentration and the percentage of motile spermatozoa and significant increase in morphologically abnormal sperm as compared to control subjects.

The ovary is also one of the highly radiosensitive organs. It contains a limited number of germ cells, which cannot be replaced if they are depleted. A loss of all the ova (approximately 4,00,000 in an adult human) results in total sterility<sup>67)</sup>. Single doses of 1.7 to 6.4 Gy have been shown to cause temporary sterility. Permanent sterility results from 3.3 to 10 Gy in a single dose or higher fractionated doses<sup>67)</sup>. Schieve *et al.*<sup>73)</sup> evaluated internal alpha-particle radiation exposure and subsequent fertility among a cohort of women formerly employed in the radium dial industry. They reported that radiation appeared to have no effect on fertility at estimated cumulative ovarian dose equivalents below 5 Sv, but above this dose statistically significant declines in the number of pregnancies and live births were observed. They further suggested that exposure to high doses of radiation from internally deposited radium reduces fertility rather than inducing sterility. Recently, Shaw<sup>74)</sup> summarized the epidemiological evidence of a potential association between a number of adverse reproductive outcomes and parental exposure to electrical and magnetic fields (EMFs) and concluded that evidence is still lacking for a strong association between women's use of video display terminals (VDT) and foetal loss/adverse pregnancy outcome and also indicated the paucity of data on other parental exposure and subsequent adverse pregnancy outcomes. The data on radiation exposure and reproductive impairment is summarized in Table 3. Experimental studies and available human data point towards reproductive impairment due to radiation exposure, which depends on the dose, duration and dose rate, etc.

### Occupation involving high temperature

Temperature plays an important role in the spermatogenesis of human beings. Therefore, nature has also kept the scrotum outside the body cavity so that the temperature of the testes may be lower than that of the body temperature. Lahdetie<sup>75)</sup> reported that active sperm production is dependent on an environment that is 4°C lower than the normal body temperature. Figa-Talmanca *et al.*<sup>76)</sup> studied the effects on sperm production of chronic

occupational exposure to high temperature in the ceramic industry. They indicated a higher prevalence of pathologic sperm profiles among the exposed subjects compared to control subjects. Bonde<sup>48)</sup> studied seventeen metal arc alloyed steel welders with moderate exposure to radiant heat but without substantial exposure to welding fume toxicants, and saw a reversible decrease in semen quality. Sperm morphology also deteriorated during six weeks of exposure and there was an increase after a break in the exposure. Zoragniotti and MacLeod<sup>77)</sup> have reported an improvement in sperm changes in men wearing a cooling device inducing chronic hypothermia of the testes. These results indicate that high temperature may have an adverse effect on spermatogenesis. The data on high temperature and reproductive impairment are summarized in Table 4. Studies pertaining to occupational exposure involving high temperature and the female reproductive system are scanty. More epidemiological and environmental studies among female workers are needed.

### Occupations involved exposure to toxic solvents and related reproductive toxicity

A large number of workers are exposed to organic solvents worldwide in various industries. Organic solvents are one of the most prevalent sources of chemical exposure in the working population. Exposure to solvents can occur in manufacturing processes, dry-cleaning, degreasing, painting and paint removal and also during printing, etc. They 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 into the foetus and could cause adverse effects on offsprings. In humans, occupational exposure to organic solvents has been related to various disorders of reproductive health. These include menstrual disorders, reduced fertility and adverse pregnancy outcomes, etc. Potential reproductive effects from occupational exposure to ethylene glycol ether are of major concern since these organic solvents have been used widely in industry. Correa *et al.*<sup>78)</sup> carried out a retrospective cohort study among workers at semiconductor manufacturing plants in the USA. Among female workers with potential exposure to mixtures containing ethylene glycol ether was associated with increased risk of spontaneous abortion and sub-fertility,



but among spouses of male workers with potential exposure to mixtures containing ethylene glycol ether, there was no increased risk of spontaneous abortion, but there was a non-significant increased risk of sub-fertility. In a study of shipyard painters exposed to 2-ethoxy ethanol (2-EE), an increased odds ratio for a lower total sperm count was found relative to non exposed workers at the same shipyard without a concurrent change in the serum LH, FSH or testosterone concentration<sup>79, 80</sup>. Thus toxicants may affect hormone production and spermatogenesis independently<sup>81</sup>. It has been reported concerning another solvent ethylene dibromide that workers exposed to this solvent had more sperm with a tapered head and fewer sperm per ejaculate than did controls<sup>82</sup>. Schrader *et al.*<sup>83</sup> reported the results of two occupational studies and mentioned that long-term EDB exposure resulted in a decline in sperm motility and viability, suggesting that whereas short-term exposure may slow sperm velocity, longer exposure may cause immotility and cell death. Furthermore, these studies suggest that the accessory sex glands may be affected by EDB exposure.

Earlier Lancranjan<sup>84</sup> studied the testicular changes in workers in an artificial fiber factory who had been exposed to CS<sub>2</sub> at various concentrations. He observed a significant higher frequency of asthenospermia, hypospermia and teratospermia in CS<sub>2</sub> poisoned workers as compared to controls. In an experimental study carried out by the author in albino rats, an increase in sperm head shape abnormality and a decrease in sperm count was observed in the CS<sub>2</sub> exposed group. Morphologically abnormal sperm were increased in the 200 mg/kg b.wt group and sperm count were decreased in both the 100 mg/kg b.wt and 200 mg/kg b.wt group<sup>85</sup>. All these changes were statistically significant. Furthermore, male mediated toxicity of CS<sub>2</sub> in females in the form of reproductive outcome was also observed in workers exposed to CS<sub>2</sub> during occupational exposure<sup>86</sup>. Vanhoorne *et al.*<sup>87</sup> studied the effects of carbon disulfide on male sexuality and reproduction and observed a significant effect of CS<sub>2</sub> exposure on libido and potency, but no effect was noted either on fertility or on semen quality. Earlier, Meyer *et al.*<sup>88</sup> studied the semen quality in workers exposed to carbon disulfides and found no significant difference between the exposed and unexposed groups in the sperm count, ejaculate volume or the morphology pattern. Pielaszek<sup>89</sup> studied the effect of carbon disulphide on menopause, the concentrations of monoamines, gonadotropins, estrogens and androgens in women working in a synthetic fibers factory and exposed chronically to carbon disulphide at concentrations of 9.36–23.4 mg/m<sup>3</sup>. Menopause was present in 16.59% in the population chronically exposed to carbon disulphide as compared with 8.05% in the normal population. The mean age at menopause in women in the CS<sub>2</sub> exposed

group was also lower than in the control group. Furthermore, the serum concentrations of estrone, estradiol, progesterone and 17-hydroxyprogesterone were significantly lower in women chronically exposed to CS<sub>2</sub>, but no significant differences were noted between the exposed and control groups in the level of FSH or LH. Earlier, Heinrichs<sup>90</sup> and Wang and Zhao<sup>91</sup> also reported an increased incidence of spontaneous abortion at a level as low as about 2 ppm (6–7 mg/m<sup>3</sup>), but a community based study of spontaneous abortion, occupation and air pollution carried out by Hemminki and Niemi<sup>92</sup> found no relationship between the carbon disulfide concentration and miscarriage rates. However, available data provide some indication that CS<sub>2</sub> may affect the reproductive system of both sexes<sup>84, 87, 89–91</sup>. Tielemans *et al.*<sup>93</sup> found an association between exposure to aromatic solvents and reduced semen quality in a case control study. Kolstad *et al.*<sup>94</sup> in a preliminary study observed a statistically significant decline in sperm density from 63.5 to 46.0 million sperm/ml during styrene exposure, where as no decline was seen in non-exposed subjects. Lindbohm<sup>95</sup> reviewed the effects of styrene on the reproductive health of women and reported that styrene has been shown to cross the human placenta. He concluded that 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. Ha *et al.*<sup>96</sup> studied the association of birth weight with maternal and paternal exposure to organic solvents in 1,222 couples employed in a large petrochemical corporation in China. They reported that maternal exposure to solvents was significantly associated with reduced birth weight, but paternal exposure to organic solvents was not similarly associated. Another study carried out among women workers in a large petrochemical complex in China by Xu *et al.*<sup>97</sup> suggested an increased risk of spontaneous abortion with exposure to petrochemicals including benzene, gasoline and hydrogen sulphides. Strucker *et al.*<sup>98</sup> carried out a study to evaluate the risk of spontaneous abortion among the wives of male workers occupationally exposed to benzene. They observed that paternal exposure to benzene did not increase the risk of spontaneous abortion. Doyle *et al.*<sup>99</sup> investigated the association between spontaneous abortion and work within dry cleaning units in the UK where perchloroethylene is used as a solvent. They found a higher risk among workers working as dry cleaning operators as compared with no work in either dry cleaning or laundry units during pregnancy, but exposure to dry cleaning as a non-operator was also not associated with any excess risk.

Recently a solvent (2-bromopropane) has been implicated for reproductive toxicity in both human and

**Table 5.** Reproductive dysfunction due to solvent exposure

| Names of the solvents      |  | Observed effects   | References   |
|----------------------------|--|--|--|
| Male Reproductive System   |  |  |  |
| 1                          | 2-ethoxy ethanol exposure during painting                        | Lower total sperm count  | Welch <i>et al.</i> <sup>79, 80)</sup>                 |
| 2                          | Ethylene dibromide   | More sperm with tapered head and lower sperm ejaculate   | Ratcliffe <i>et al.</i> <sup>82)</sup>                 |
|                            |  | Decrease in sperm motility and viability   | Schrader <i>et al.</i> <sup>83)</sup>                  |
| 3                          | Carbon di sulphide   | Higher frequency of asthenospermia, hypospermia and teratospermia  | Lancranjan <sup>84)</sup>                              |
|                            |  | Significant effect on libido and potency   | Vanhoorne <i>et al.</i> <sup>87)</sup>                 |
|                            |  | No significant change in sperm count or morphology   | Mayer <i>et al.</i> <sup>88)</sup>                     |
| 4                          | 2-bromopropane   | Oligospermia and azoospermia   | Kim <i>et al.</i> <sup>100)</sup>                      |
| 5                          | Styrene  | Sperm count decline  | Kolstad <i>et al.</i> <sup>94)</sup>                   |
| 6                          | Exposure to aromatic solvent                                     | Reduced semen quality  | Tielemans <i>et al.</i> <sup>93)</sup>                 |
| Female Reproductive System |  |  |  |
| 1                          | 2-bromopropane   | Ovary dysfunction accompanying amenorrhea  | Kim <i>et al.</i> <sup>100)</sup>                      |
| 2                          | Carbon di sulphide   | Early menopause and reduction of serum concentration of estrone, estradiol, progesterone, 17-hydroxyprogesterone | Pieleszek <sup>89)</sup>                               |
|                            |  | Increase incidence of spontaneous abortion   | Heinrich <sup>90)</sup> , Wang and Zhao <sup>91)</sup> |
|                            |  | No relationship between CS <sub>2</sub> concentration and miscarriage  | Hemminki and Niemi <sup>92)</sup>                      |
| 3                          | Exposure to organic solvent in petrochemical industry            | Maternal exposure leads to reduced birth weight  | Ha <i>et al.</i> <sup>96)</sup>                        |
| 4                          | Exposure to ethylene glycol ether in semiconductor manufacturing | Female sub fertility   | Chen <i>et al.</i> <sup>108)</sup>                     |
| 5                          | Toluene  | Reduced fecundity  | Pleng-Bonig and Karmaus <sup>110)</sup>                |

experimental studies. A report on the mass intoxication of workers at an electronic company in Korea reported that 17 out of 25 female workers have an ovary dysfunction accompanying amenorrhea. Six out of eight male workers had oligospermia or azoospermia. This report further indicated that 2-bromopropane (2-BP) might be a possible causative chemical for reproduction and haematopoietic toxicity<sup>100)</sup>. The animal studies conducted by Ichihara *et al.*<sup>101)</sup> lend support to the reproductive and hematopoietic toxic effects of 2-bromopropane as observed in a human study. They observed that 2-bromopropane has specific effects on spermatogenesis and hematopoiesis in rats and mentioned that spermatogenesis seemed more vulnerable to 2-bromopropane and less reversible than hematopoiesis. Omura *et al.*<sup>102)</sup> estimated based on the histological studies that 2-bromopropane had no direct adverse effects on spermatocytes but affected the spermatogonia. Later Yu *et al.*<sup>103)</sup> concluded that testes are the main target organs for 2-BP toxicity and also affect the hematopoietic system and this induces leucopenia and normocytic anemia. Furthermore, studies on 2-bromopropane conducted by

Son *et al.*<sup>104)</sup> in rats also suggest that high doses of 2-BP can decrease spermatogenesis by adversely affecting spermatogonia followed by depletion of spermatocytes, spermatids and spermatozoa with subsequent testicular atrophy. Recently, Li *et al.*<sup>105)</sup> observed that at a dose of 2-BP 1,355 mg/kg/d, significantly decreased the weight of the body and testes, epididymes, seminal vesicles and prostate, as well as daily sperm production. Further, atrophy of the seminiferous tubules accompanied with degeneration of germ cells such as spermatogonia, spermatocytes, and elongated spermatids was observed in the testis of rats exposed to 405 and 1,355 mg/kg/d of 2-BP. These data on 2-BP clearly point towards reproductive toxic effects of this compound. Further, Kamijima *et al.*<sup>106)</sup> studied the ovarian toxicity of 2-bromopropane in rats and concluded that 2-bromopropane is as toxic to the female reproductive system as it is to the male. They further suggested that the amenorrhoea observed among Korean workers in an electronics factory could be primarily attributable to 2-bromopropane exposure. Lim *et al.*<sup>107)</sup> also reported that 2-BP treatment decreased the ovarian weight and fertility and tended to

decrease the number of pups born, depending on the dose of 2-BP.

Based on personal interviews of the workers, Chen *et al.*<sup>108)</sup> observed that ethylene glycol ether may cause female sub-fertility among the workers. Ng *et al.*<sup>109)</sup> studied the menstrual disorders in 231 female production workers exposed to toluene (range 50–150 ppm: mean 88 ppm) in a factory manufacturing audio speakers and compared the frequencies with those of a control group of 58 female production workers in other departments in the same factory who had little or no exposure to toluene (0–25 ppm) and also with another control group from a community of working class women. Dysmenorrhoea seemed to occur more often in the women highly exposed to toluene compared with women of a community working class, but not compared with factory controls with low exposure to toluene. They concluded that it is uncertain whether dysmenorrhoea was associated specifically with exposure to toluene, as other behavioral and work related factors may also result in dysmenorrhoea. Pleng-Bonig and Karmaus<sup>110)</sup> examined the possible influence of exposure to toluene on human fertility and reported that low daily exposure to toluene in women seemed to be associated with reduced fecundity. The data on solvent exposure and reproductive dysfunction are summarized in Table 5. These results suggest that organic solvents in general may play a role in affecting both male and female reproductive systems.

### **Other occupational situations responsible for reproductive dysfunction**

In addition to these, there are a number of other occupational situations where workers are reported to have adverse effects on reproduction. Male dentists and anesthetists are at increased risk of fathering a child with a congenital malformation due to occupational exposure to trace anesthetic gases<sup>111, 112)</sup>. An epidemiological reproductive study conducted among male workers in a rubber factory indicated a significant increase in the frequency of abortions and congenital malformations in the families of exposed workers as compared to control groups. On the basis of reproductive data they suggested that undue exposure of men to rubber chemicals resulted in genetic damage<sup>113)</sup>. De Celis *et al.*<sup>114)</sup> determined the semen quality of workers in the rubber industry occupationally exposed to hydrocarbons. They reported that damage to the spermatogenic process resulting from exposure to hydrocarbons was revealed by an increased rate of abnormalities in the semen of exposed workers compared with unexposed workers.

Dioxin, an industrial byproduct, is commonly considered one of the most toxic man made substances. Earlier, research has shown that high serum concentrations of dioxin in parents from Seveso, Italy, were linked to a relative increase in the number of female

births compared to male after exposure to dioxin<sup>115)</sup>. Mocarelli *et al.*<sup>116)</sup> continued the study to find the effect of serum dioxin concentrations on the sex ratio of offspring in the Seveso population. They concluded that exposure of men to dioxin is linked to a lowered sex ratio which may persist for years after exposure. They also mentioned that the average concentration of dioxin in fathers in this study was similar to the doses that induced reproductive impairments in rats, and about 20 times the estimated average concentration of dioxin currently found in human beings in industrialized countries. Ryan *et al.*<sup>117)</sup> investigated the sex ratios of children of Russian pesticide workers who produced the biocide trichlorophenol and the herbicide 2,4,5-trichlorophenoxy acetic acid and exposed to dioxin during the production of these chemicals. They observed that human exposure of these pesticide producers to high levels of dioxins is associated with the birth of more girls, but only in the case of paternal exposure. In contrast to these studies, Karmaus *et al.*<sup>118)</sup> reported that paternal PCB exposure was linked to a higher population of male offsprings. Schnorr *et al.*<sup>119)</sup> studied the wives of 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) exposed chemical workers and wives of non-exposed neighborhood referents. No association between the paternal TCDD level at the time of conception and spontaneous abortion was observed among pregnancies fathered by workers with TCDD levels of <20 to 1,120 ppt compared to pregnancies fathered by referents. The sex ratio [males/(males + females)] of offspring also did not differ with TCDD exposure. They also did not find an association between the paternal serum TCDD level and spontaneous abortions and the sex ratio of offsprings in this study. Epidemiological studies of large populations have demonstrated increased frequency of spontaneous abortions in women whose husbands were working as motor vehicle mechanics<sup>120)</sup>. Data available on the association of chemical exposure and adverse reproductive outcome in humans are equivocal and sometimes controversial due to a lack of exposure parameters or proper designing of the study. The exact role of male mediated toxicity in such adverse effects as abortions, congenital malformations and pre-term delivery, etc. is not yet fully understood, but this may be due to the exposure of pregnant females through seminal fluid and also to the carry home exposure to pollutants by the males.

### **Environmental endocrine disruptors and reproductive health**

During the last two to three decades, there have been widespread growing concerns and public debate over the potential adverse effects that may result from exposure to persistent chemicals likely to cause endocrine disruption. In recent years, scientists have raised concern

**Table 6.** Reproductive dysfunction in males and females due to other Occupational situations

| Names of the occupations and chemicals |  | Observed effects   | References   |
|--|--|--|--|
| Male Reproductive System               |  |  |  |
| 1                                      | Male dentists and anesthetists exposed to traces of anesthetic gases | Increased risk of fathering a child with congenital malformations                  | Cohen <i>et al.</i> <sup>111)</sup> , Guirguis <i>et al.</i> <sup>112)</sup> |
| 2                                      | Welders  | Deterioration in semen quality even though sperm count in normal range             | Kumar <i>et al.</i> <sup>50)</sup>   |
|  |  | No major hazards for human spermatogenesis   | Bonde and Ernst <sup>51)</sup>   |
|  |  | No difference in semen quality   | Jelnes and Kundsén <sup>52)</sup>  |
| 3                                      | Workers in rubber factory  | Increased abortion and congenital malformations in the families of exposed workers | Hemaprasad <i>et al.</i> <sup>113)</sup>                                     |
| 4                                      | Workers in rubber industry exposed to hydrocarbons                   | Increased rate of abnormalities in semen   | De Celis <i>et al.</i> <sup>114)</sup>                                       |

about the indiscriminate use of persistent synthetic chemicals in various walks of life and their possible health consequences. These persistent synthetic chemicals released into the environment might have affected the development and/or function of the reproductive, endocrine, immune and nervous systems of various animal species. Human beings can also be exposed to these chemicals during their occupation or day-to-day activity. The persistent nature of these chemicals in the environment and bioaccumulation in the body raises the possibility of long-term deleterious effects. Many hormone-disrupting chemicals might persist in the environment for decades together. Concern regarding exposure to endocrine disruption is mainly due to 1) Adverse effects observed in certain wildlife, fish and ecosystems 2) The increased incidence of certain endocrine related human diseases and 3) Endocrine disruption resulting from exposure to certain environmental chemicals observed in experimental animals<sup>121)</sup>. Scientists believe that some of these environmental exogenous chemicals may bind with hormone receptors in the body and might inhibit the activity of natural hormones or elicit hormone-like effects by themselves or circulate in the body, and in turn interfere in various essential body functions and could affect health including the reproductive and endocrine systems. Recently, Crisp *et al.*<sup>29)</sup> broadly defined the endocrine disruptors as exogenous agents that interfere with the production, release, transport, metabolism, binding action or elimination of natural hormones that are responsible in the body for the maintenance of homeostasis and the regulation of the developmental process and/or behavior. Many structurally different chemicals have been shown to have endocrine disruptive effects reported either *in vivo* or *in vitro* and cannot be predicted as endocrine disrupting agents on the basis of their structure.

Hormones play an important role in the proper development of the growing foetus and also in adulthood.

Disorders of any endocrine systems, involving both over and under active hormone secretion, result inevitably in disease, the effects of which may extend to many different organs and functions and are often debilitating or life threatening<sup>121)</sup>. It is known that the foetus is vulnerable even to the minutest concentrations of chemicals. Some of these chemicals pass from mother to offspring, through the womb and breast milk in mammals and via the egg in reptiles, amphibians and fish, which could affect their offsprings. The timing of exposure to these chemicals during the critical period of development is as important as the dose and duration of exposure. Exposure to very small amounts of a hormone-disrupting chemical at an important period of development can be more deleterious than greater exposures at other times or in adult life. Very low concentrations of these chemicals raise the possibility of having adverse effects on humans or animals, but in a real life scenario, living beings are exposed to a mixture of such chemicals, so that there is the possibility that the interaction of certain persistent chemicals might produce synergistic effects. Very recently, Aoki<sup>122)</sup> suggested that humans are exposed to dioxins from the environment along with various other compounds, e.g., polyaromatic hydrocarbons and heterocyclic-amines, which can act synergistically, so the endocrine disrupting activities of the dioxins are possibly enhanced by them. IPCS documented that the issue of the dose-response relationship is perhaps the most controversial issue regarding EDCs<sup>121)</sup>. A recent workshop on this aspect concluded that although low-dose effects may be occurring, these effects often are not replicated consistently, and the toxicological significance of the reported effects is not known<sup>123)</sup>.

A number of laboratory studies have demonstrated that exposure of foetuses to endocrine disrupting chemicals can profoundly disturb organ differentiation<sup>28, 124)</sup>. Organs that appear to be at particular risk for developmental abnormalities in offspring due to maternal exposure are

those with receptors for gonadal hormones; in female fetuses these include the mammary glands, fallopian tubes, uterus, cervix and vagina and in male fetuses it includes the prostate, seminal vesicles, epididymis and testes. In both sexes the external genitalia, brain, skeleton, thyroid, liver, kidneys and immune system are also targets for endocrine disrupting chemicals reported by various investigators<sup>125–127</sup>. Now some scientists believe that hormone-disrupting chemicals have contributed to various health and reproductive problems in men and women, including a rising incidence of breast, prostate and testicular cancers, declines in sperm count, an increasing incidence of endometriosis, and also an increase in genital defects, etc. (debate is still going on), but the data are inconclusive and need confirmation before reaching any firm conclusion.

The data on the role of endocrine disrupting chemicals in reproductive abnormalities in wildlife and other animals are accumulating. Guillette *et al.*<sup>128</sup> reported a reduction in penis size and serum testosterone levels in a juvenile alligator population in Lake Apopka, Florida, USA, and these phenomena have been attributed to the contamination of the lake by the DDT-metabolite p,p'-DDE. They further reported that alligators in Lake Apopka have increased concentrations of p,p'-DDE, dieldrin, endrin, mirex, oxychlordane, DDT and PCBs<sup>129</sup>. Earlier, Fox<sup>130</sup> reported that newly hatched herring gull chicks in Lake Ontario, USA, had an altered reproductive system; in a region highly contaminated with DDT. Male chicks had oviducts and gonads resembling the ovaries and oviduct system of female birds developed abnormally. Further there are reports that the sex ratio has been affected in several north American gull populations, resulting in an over abundance of females in some breeding colonies<sup>121</sup>. But several questions remain to be answered before reaching any conclusion about the observed effects in gull populations. Whether these are due to endocrine disruptors or different sensitivity of males and females to the exposed endocrine disrupting chemicals or their excretion from the body. Recent researches indicated that many chemicals mimic female like hormones or some of them are anti-androgenic. Kelce *et al.*<sup>131</sup> reported that 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. Taylor *et al.*<sup>132</sup> reviewed the literature on endocrine disruption in wildlife and suggested that in fact, the evidence showing that such chemicals actually do mimic (or antagonize) the action of hormones in the intact animal is limited. In only a few cases laboratory studies have shown that chemicals that mimic hormones at the molecular level (*in vitro*) also cause reproductive dysfunction *in vivo* at environmentally relevant concentrations. They further mentioned that the reported

studies on wildlife populations of animals are limited to a very few animal species and these are centered on localized hotspots of chemical discharges.

There are reports regarding an apparent drop in semen quality from different parts of the world particularly from western countries<sup>133, 134</sup>. A systematic meta analysis of 61 studies, which included 14947 normal men, was undertaken by Carlson *et al.*<sup>133</sup> It showed a significant decrease in the sperm concentration from 113 to 66 million /ml, and a sperm volume decline from 3.40 to 2.75 ml, over the period 1938–1990. These findings sensitized the scientific community and have stimulated further research. Gopalkrishnan<sup>135</sup> from Bombay, India, also mentioned a definite trend to a decline in semen quality. She reported that there is a decrease in the mean percentage of normal morphology with less than thirty percent normal forms. Swan *et al.*<sup>136</sup> reported that there was no evidence of a decline in semen quality in non-western countries while they observed a significant decline in Europe and United States, but other investigators reported no such change in semen quality<sup>137, 138</sup>. At present the data available on human semen parameters are still under extensive debate, and both exposure and effect quality data are needed in order to reach any conclusion. Recently, IPCS also mentioned that a global trend in declining semen quality is not supported by the current data. 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<sup>121</sup>.

Sharpe and Skakkeback<sup>139</sup> postulated that an apparent drop in the sperm count may be due to the developmental exposure to estrogenic xenobiotics. Denzo<sup>140</sup> suggested that although environmental chemicals have weak hormonal activity, their ability to interact with more than one steroid sensitive pathway, provides a mechanism by which their hazardous nature can be augmented. He further reported that numerous potential agonists/antagonists working together through several steroid-dependent-signaling pathways could prove to be hazardous to human reproductive health. For many of the endocrine systems, it appears that a programme is established during fetal/neonatal development in mammals and that an abnormal environment at this stage of life can result in permanent misprogramming<sup>141, 142</sup>. Studies that clearly indicate exposure and effects measures are scanty on environmental endocrine disruptors. This limits the ability to draw firm conclusions from the available studies even though some animal data are available. Recently, Kumar *et al.*<sup>143</sup> reported that there is growing evidence that a large number of environmental chemicals have the potential to cause adverse effects and/or alter the functions of the endocrine system which might cause adverse health effects to an organism or its progeny. Wada<sup>144</sup> reviewed the toxicity studies on the major endocrine disruptors and reported

that only dioxins, which are endocrine in the broad sense, cause toxicity in humans, whereas toxicity data on other agents have only been obtained in animal experiments. No comprehensive studies are available in humans correlating reproductive dysfunction with exposure to markers of these chemicals. Daston *et al.*<sup>145)</sup> also concluded that estrogenicity is an important mechanism of reproductive and developmental toxicity, but there is little evidence at this point that low level exposures constitute a human or ecologic health risk. Very recently, Skakkeback *et al.*<sup>146)</sup> summarized existing evidence supporting 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. Furthermore, they suggested that TDS is a result of disrupting embryonic programming and gonadal development during foetal life. Therefore it can be inferred that exposure to endocrine-disrupting chemicals may have little effect on the exposed adult organism, but the offspring of that organism may suffer repercussions. Nevertheless, this hypothesis remains to be probed on the basis of more data to be generated in future studies. Recently, Massaad *et al.*<sup>147)</sup> suggested several possible mechanisms for the toxicity of xenobiotic compounds that display hormonal activity. They reported 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 a wrong time or place, and thus trigger developmental malformations. They also suggested that natural steroid hormones bind to serum proteins, such as SSBG (Serum steroid binding globulin). Interestingly, xenohormones also bind poorly to SSBG and thus the available concentrations of natural hormones in a free state is relatively high, which favors their potency. Further, they suggested that the half-life of steroid hormones is limited by their P-450 dependent metabolism, whereas xenobiotics appear to have a much higher stability. Hence the presence of persistent chemicals during the developmental period might have profound effects on the offspring. All the available data suggest that EDCs can act at multiple sites via multiple mechanisms of action, but the link determining the observed adverse effects due to EDCs in humans and wildlife is weaker, as most of the data are limited to highly exposed populations.

### **Intervention or reducing chemical exposure**

Keeping in view the deleterious reproductive hazards associated with certain occupations, action is needed to protect people from hazards and to prevent disorders of reproduction. We know that programs to prevent infectious diseases have been highly successful by

adopting immunization programs, but occupational reproductive disorders/diseases can be successfully controlled only through aggressive prevention programs and may even be eradicated. Prevention of occupational disorders of reproduction, is much more problematic due to gaps in the existing knowledge as well as other non-occupational factors, which cannot be separated from occupational factors. Because of scanty data and gaps in existing knowledge, the prevention strategy should focus on research to find reproductive toxicants by conducting well-planned animal studies. The prevention of most disorders of reproduction in humans, however, will require successful research programs to improve our understanding of reproductive and developmental biology and to identify etiologic agents and populations at risk. The assessment of risk to humans is absolutely necessary for such chemicals that have already proved toxic to the reproductive system in animal studies. Infertile cases due to DBCP exposure is one example where attention was given to animal reproductive toxicity data only after workers became infertile.

### **Limitations to documenting occupations hazardous to reproduction**

Occupations which are hazardous to reproduction are generally assessed on the basis of years of service, possible exposure agents based on the chemical used in the industry as well as industrial environmental monitoring and adverse reproductive outcomes such as abortion, poor semen quality, congenital malformations, etc. Nevertheless, the biological exposure monitoring data along with effect parameters are too scanty to indicate exactly which compound/chemical or factor is responsible for the reproductive impairment. Furthermore, various other confounding factors such as malnutrition, infections, smoking, indoor pollution, etc. are also involved in reproductive dysfunction. In addition, reproductive impairment in some occupations may be reversible, whereas in others the effect may be irreversible. Tas *et al.*<sup>148)</sup> also reported in his review that it is often difficult to elucidate the role of a single agent because occupational exposure conditions are often complex and various confounding factors related to lifestyle or the socioeconomic state may also affect sperm quality, fertility, or pregnancy outcomes. Furthermore, reproduction is also a sensitive issue for workers as well as for their employers. Nevertheless, research on the association, if any, between occupational exposures and the reproductive system, including growth and development, is relatively new and there are significant gaps in the knowledge of the factors responsible for reproductive toxicity and their mechanisms of action. If the exposure is to a known reproductive toxicant and the exposure level is significant then workplace engineering modification and changes in job practices may be helpful

in reducing the exposure level.

Mechanisms underlying reproductive toxic alteration are complex. Most of the xenobiotic substances are demonstrated to be more toxic to the male reproductive process than to female, but it is not clear whether this is due to differences in toxicity or that it is easier to study sperm than oocytes. Effects of chemicals on reproduction may be induced directly by a chemical itself on reproductive organs or indirectly through influence in altering hormonal regulation. 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 gland and the testes. Toxicants that damage the Leydig cells can lead to reduced secretion of testosterone, which in turn affects Sertoli cell function and spermatogenesis. Most reproductive toxicants are thought to act directly on the testes. 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. Furthermore, potential human exposure, suggestive evidence of possible deleterious effects on the developing reproductive system, and sensitivity of the reproductive organs, suggest that there are significant grounds to be concerned about the indiscriminate use of these chemicals.

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