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Review Article

The Action of Oil-Related Environmental Pollutants on Male Reproductive System

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Abstract

The low-weight aromatic hydrocarbons benzene, toluene, ethylbenzene, m/p-xylene, and o-xylene (BTEX), are among the most common hazardous sources of environmental contamination. The present review is the first summarization the data obtained during epidemiological, animals and cell culture studies concerning BTEX action on different aspects of male reproduction-testicular cell apoptosis, spermatogenesis, cytogenetics, pituitary and peripheral hormones and intracellular signaling systems. Analysis of the available literature demonstrates that BTEX can exert hazardous effects on various reproductive sites, including the pituitary-gonadal axis, hormone receptors and intracellular signaling molecules, testicular cell apoptosis, spermatogenesis and fertility. There are indications, that BTEX reproductive effects could be due to the ability of BTEX to affect embryonal gonads, to induce testicular cell mutagenesis and destroy chromosomes, to promote accumulation of free radicals, to affect hormones and hormonal receptors, cell cycle and CNS structures regulating reproduction, but only the role of free radicals in mediating BTEX action on male reproduction has been proven by experiments yet. Some approaches to prevent negative action of BTEX are outlined.

Keywords: Oil pollutants; Testis; Sperm; Hormones; Fecundity

The Oil-Related Environmental Pollutants and their Physiological Effects

Aromatic hydrocarbons including benzene, toluene, ethyl benzene, xylene (BTEX) are retrieved during fossil fuel extraction. They are used as solvents in consumer and industrial products, as gasoline additives, and as intermediates in the synthesis of organic compounds for many consumer products. Unfortunately, BTEX are persistent organic pollutants, released into the environment mainly by exploration activities of petroleum industry. BTEX are especially dangerous because of their (1) multiple sources of contamination in the environment (e.g., oil production, oil refrigeration, oil transportation, the production of petroleum, solvents, coal-derived products, traffic, tobacco smoking, voluntary inhalation as drugs of abuse, cosmetics etc.), (2) relatively high solubility in water and air and therefore easy migration and distribution in the environment and easy transport into the cells, (3) highly solubility in lipids and thus readily absorbed from environment in gastrointestinal tract and by all cell membranes (4) low physical, chemical and biological degradation in ecosystems, and (5) multiple toxic influences and (5) accumulation and low degradation in organisms [1-6].

BTEX can express toxic [2,6-10], mutagenic, carcinogenic [11], embryotoxic and teratogenic [9,12-14], growth retarding [7,8,14-16], metabolic [7,8,16], and neuromodulatory [11,17,18] effects. Presence of alkyl side chain in toluene, ethyl benzene and xylene but not in benzene induce oxidative properties of these molecules and differences in their degradation in organism. Health effects significantly associated with ambient exposure to BTEX included cardiovascular disease, respiratory dysfunction, asthma, sensitization to common antigens, and more [2,19] including reproductive disorders.

Reproduction and Its Gender-Related Susceptibility to Environmental Pollutants

The most dangerous effects of BTEX could be their influence on the most important biological process-reproduction. Reproduction in both sexes is regulated by similar multi-level system of regulatory molecules. Information from environment reach central nervous system receptors and then monoaminergic structures regulating hypothalamic peptides (kisspeptin, leptin, gonadotropin-releasing hormone etc.). These molecules are controlling release of pituitary gonadotropins and other regulators of peripheral reproductive organs. Reproductive organs in turn produce signaling molecules responsible for their self-regulation (autocrine/paracrine regulation) and for (endocrine) regulation of their upstream regulatory structures [20]. BTEX can affect signaling molecules at all regulatory levels [21].

Female reproduction is especially susceptible to BTEX action [1,3,22]. The available evidence for character, sites and mechanisms of BTEX action on female reproductive system has been recently summarized [23]. In contrast, the action of BTEX on male reproductive system has not been reviewed yet. The present review is the first attempting to summarize the data obtained during epidemiological, animals and cell culture studies concerning BTEX action on male reproductive system at different regulatory levels. The details concerning age-, dose- and time-dependent aspects of BTEX action on male reproductive processes have been omitted because they could be found in the related publications.

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The Oil-Related Environmental Pollutants Affect Testicular and Sperm Morphology and Fecundity

The occupational exposure of workers to benzene, xylene and toluene was manifested by accumulation of these BTEX in both blood and plasma, as well as with marked decrease in sperm vitality and motility [24]. The association between exposure of workers to benzene and their sperm count and quality [24,25], raising concerns for worker infertility and spontaneous abortions as well as mental retardation and inherited defects in their children [26] indicates negative influence of benzene on male reproduction. This hypothesis based on epidemiological studies was confirmed by animal experiment with benzene administration. Male rabbits drinking water containing benzene had reduced mating desire/ability, sperm quality (acrosomal dysgenesis and nuclear malformations) [27], decrease in weights of seminal vesicles, in the diameters of testicular tubules and Leydig cells nuclei, in number of spermatogonia and spermatocytes, appearance in multinucleated giant cells, cytoplasmic vacuolization, pyknosis of nuclei, chromatolysis, desquamation and dissolution of germ cells in tubular lumen [28] and apoptosis in Sertoli cells [29]. Consumption of this water resulted occurrence of intratubular germ cell neoplasia in rabbits -the precursor lesion of germ cell tumors in men, and acrosome malformations [30]. Benzene induced also histopathoilogical changes in mice Leydig cells and seminiferous epithelium [31]. Inhalation of ethylbenzene, a solvent structurally similar to benzene, induced rat and mice testicular tubular neoplasms and increased incidence of testicular tumor [32,33].

Drinking of water containing xylene reduced rat epididymal sperm reserve, testicular sperm reserve and testicular weight. Histological study revealed xylene-induced testicular degeneration characterized by depopulation of seminiferous tubules and depletion or degenerative changes in the spermatogenic cells [34,35]. On the other hand, musk xylene used in fragrances applied dermally to rats did not caused their testicular atrophy [36]. National Toxicology Program (1990) failed to detect the influence of toluene inhalation on rat and mouse sperm quality and fecundity. Moreover, inhalation of toluene or xylene, did not affect morphology of vas deferens or epididymis sperm, fertilization, and it did not induce testicular atrophy [37]. Finally, toluene and xylene inhalation were able to protect from rat testicular atrophy induced by inhalation of n-hexane [37] and ethylene glycol [38]. On the other hand, there are reports concerning the ability of toluene administration to induce rat testicular cell apoptosis [39] and to reduce rat spermatogenesis and seminiferous tubule diameter [40]. Taken together, the majority of the published reports demonstrate that all benzene and xylene can induce testicular cell atrophy and malformation leading to infertility, although some studies demonstrated no or even protective action of xylene and toluene on male reproductive processes. The qualitative differences in reported effect of BTEX on testicular atrophy could be due to different experimental models and/or different doses of administrated BTEX. Therefore, further studies are needed to establish even general character of BTEX effect on testis.

Do Oil-Related Environmental Pollutants Affect Embryonal Testicular Functions?

Maternal exposure to toluene reduced the synthesis and secretion of testosterone in fetal testes from rats demonstrating that this hydrocarbon can inhibit fetal testicular androgen production [41] (see below). Epidemiological studies revealed association between maternal occupational exposure to toluene and occurrence of testicular germ cell tumors in the male offspring [42] suggesting that this hydrocarbon can induce testicular cancerogenesis in embryos. To our knowledge, the paternal influence of BTEX on embryogenesis of the offspring has not been studied yet.

The Oil-Related Environmental Pollutants Affect Male Hormones

Inhalation of toluene or xylene, did not affect rat testicular androgen biosynthetic capacity of testis, testosterone and noradrenaline blood concentration [37]. On the other hand, drinking of water containing xylene reduced rat serum testosterone levels [34]. Moreover, toluene reduced the secretion of testosterone and the expression of of 3beta-hydroxysteroid dehydrogenase, but not of cytochrome P450 cholesterol side-chain cleavage, cytochrome P450 17alpha-hydroxylase/c17-20 lyase and 17beta-hydroxysteroid dehydrogenase, the key steroidogenic enzymes in rat fetal testis [41]. Male rabbits drinking water containing benzene had reduced serum LH level and reduced testosterone release in response to exogenous human chorionic gonadotrophin [27]. Addition of benzene to rat pituitary adenoma cell culture increased growth hormone secretion and modulated several intracellular signaling pathways related to somatostatin receptor and estrogenic pathways [43]. Moreover, exposition of pubertal rats to xylene suppressed activity of their testicular steroidogenic enzymes and testosterone release [35]. These observations indicate that BTEX can affect release of pituitary and steroid hormones and their intracellular signaling pathways controlling reproductive processes.

Possible Mediators of Oil-Related Environmental Pollutants Effect on Male Reproduction

In contrast to female reproductive system, the direct evidence concerning mechanisms of BTEX action on male reproductive system is almost absent. Therefore, it is insufficient evidence to outline the concept integrating primary and secondary mechanisms of BTEX action on male reproduction at various regulatory levels. It might be however proposed, that BTEX can influence testicular function *via* four basic mechanisms-(1) activating steroid hormones receptors, (2) inducing testicular cell mutagenesis, (3) inducing oxidative stress, (4) affecting cell cycle and (5) affecting Central Nervous System (CNS) regulators of reproduction.

The first hypothesis explains the action of BTEX (as endocrine disrupters) on reproduction by their action on steroid hormones production and reception. Estrogenic activity of benzene present in environment [44] could be principally responsible for current male feminization and the resulted decrease in their sperm quality. On the other hand, large-scale studies did not confirm the hypothesis of endocrine disruptor effect on male reproductive disorders. No association between *in utero* exposure to estrogenic endocrine disrupters (including hexachlorobenzene) and risk of cryptorchidism, hypospadias, low sperm counts and testicular cancer was found [45]. These testicular pathologies in newborns can be induced by

genetic defects in androgen production [46]. Furthermore, the action of BTEX on androgen biosynthesis has been demonstrated (see above). Nevertheless, there no direct evidence for BTEX action on male reproductive system *via* action on either estrogen or androgen receptor has been obtained yet.

The other hypothesis, concerning ability of BTEX to reduce male sperm quality *via* its mutagenic action is supported by observation of association between occupational exposure of workers to benzene and increased incidence of chromosomally defective sperm. These chromosomal aberrations include chromosomal deletions that cause infertility, mental retardation and congenital malformations [25,26,47]. Nevertheless, the data of epidemiological association have not been validated by suitable experiments yet.

On other mechanism of BTEX-induced male infertility could be the ability of BTEX to promote oxidative stress [48]. This stress can induce apoptosis in various cell types [49] and cause lipids, proteins, and DNA damage, weaken sperm function, semen quality, fertilization rates, sterility, failure of implantation, impaired embryonic development, recurrent pregnancy loss and poor assisted reproductive technology outcomes. Therefore, oxidation-reduction potential - a direct evaluation of the redox balance between reactive oxygen species and antioxidants can be useful marker to characterize sperm quality and to predict its fertility [50]. Benzene-induced apoptosis in rat Sertoli cells was associated with elevation in reactive oxygen species generation, decrease in antioxidant enzyme, whilst reactive oxygen species scavenger prevented these benzene effects [29]. Xylene promoted markers of oxidative stress and apoptosis in rat testis [35]. Testicular antioxidant enzymes were affected by toluene too [39], whilst the antioxidant thymoquinone was able to prevent the adverse effect of toluene on rat testicular morphology and cell death [40]. These observations demonstrate that benzene and toluene can induce testicular cell death *via* promotion of increased reactive oxygen species accumulation, and that antioxidants can be useful for prevention of negative BTEX influence on testis.

The information concerning BTEX action on cell cycle of testicular cells is insufficient. Nevertheless, Zhu et al [35] observed that rat exposure to xylene reduced the expression of genes related to cell proliferation GSK-3β, ERK1/2, AKT1, and SIRT1 in their testis.

Benzene exposure reduced LH level in rat plasma [27]. On the other hand, Zhu et al. [35] did not found xylene influence on rat plasma LH and FSH levels. Toluene exposure is able to affect antioxidants and apoptosis not only in rat testis, but also in CNS (brain cortex and cerebellum) [39]. Therefore BTEX can potentially affect testicular cells not only directly, but *via* CNS. Nevertheless, the existence of this mechanisms of BTEX action on male reproductive processes requires experimental validation.

Therefore, only one mechanism of BTEX action on male reproduction, *via* induction of oxidative stress, was more or less experimentally validated. The existence of other mechanisms (BTEX as endocrine disrupters, as mutagenes, as regulators of cell cycle and as CNS) requires detection by further studies.

Conclusions and Possible Direction of Future Studies

The analysis of the available literature demonstrates substantial variability in the available data concerning BTEX action on male reproductive systems and processes. Such variation could be due to kind of studied BTEX, ways and doses of their administration, differences in efficiency of epidemiological, animal and *in-vitro* studies, the animal species, analyzed sites and read-outs. Nevertheless, the majority of available reports demonstrates that BTEX can exert negative effects on various male reproductive sites, including the pituitary-gonadal axis, their signaling molecules and receptors, spermatogenesis, fertility, and the viability of offspring. The BTEX influence on CNS and embryogenesis of the offspring is possible, but no direct evidence for such influence in males are available yet. The sites of BTEX action on male reproductive processes and reproductive disorders are summarized in Figure 1. The BTEX

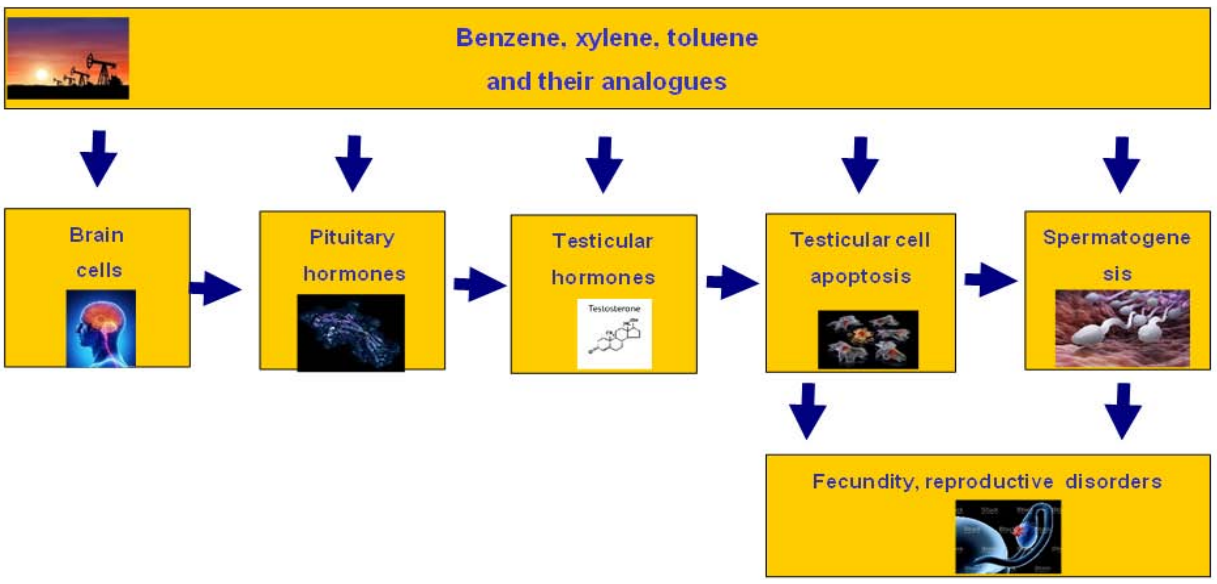

Figure 1: The known targets of oil-related contaminants in male reproductive system (simplified). Explanations are in the text.

effects could be due to the ability of BTEX to induce mutagenesis and destroy chromosomes, to affect the accumulation of free radicals, to affect hormones and hormonal receptors regulating reproduction, to influence cell cycle and central nervous system, although these mechanisms require still strong experimental validation.

Functional interrelationships between different BTEX effects are possible. For example, BTEX action on the pituitary gonadotropins can affect multiple gonadotropin-regulated male reproductive processes (steroidogenesis, spermatogenesis, fecundity etc.). It is also possible that non-specific cytotoxic, oxidative and mutagenic action of BTEX can destroy reproductive processes at once at multiple regulatory levels.

Although understanding the effects of BTEX on reproduction is very important from both theoretical and practical (e.g., medical, ecological, etc.) viewpoints, the current available knowledge is poorly understood and superficial. Not all BTEX hydrocarbons are studied in relation to the main reproductive processes. Rather, most available data were obtained on only two species: rats and humans. Finally, little is known about how to prevent or neutralize the negative effects of BTEX on reproduction. The most efficient ways to reduce negative effect of BTEX now are prevention their leak into the environment, their bioremediation by using microorganisms to treat this waste and mineralization of contacts with they [6]. Furthermore, some biomedical approaches can reduce adverse effects of BTEX when their contact animals and humans. The protective action of antioxidant has been demonstrated. It is known that some effects of stress on ovarian function could be prevented or neutralized with stem cell therapy, hormones, growth factors, pharmacological and genomic regulators of intracellular signaling molecules, some cDNA, siRNA, and miRNA constructs or plants containing antioxidants and other adaptogenes [23] or changes in metabolic state [23,51,52]. For example, high body fat content can reduce susceptibility of mice [23] and cow [51,52] ovarian cells to BTEX, and consummation of tobacco and coffee can prevent reduction in fertility of women subjected to occupational exposure to toluene [53,54]. Unfortunately, such studied have not been performed on males yet. A better understanding of the physiological, genetic, endocrine, and intracellular aspects of BTEX action could advance characterization, application, prevention and neutralization of the BTEX effects and for treatment of BTEX-induced reproductive disorders.

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