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Review

Influence of oil-related environmental pollutants on female reproduction

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ABSTRACT

The petroleum low-weight aromatic hydrocarbons benzene, toluene, ethylbenzene, m/p-xylene, and o-xylene, also known as BTEX, are among the most common hazardous sources of environmental contamination. This paper reviews the available data concerning the effects of BTEX on different aspects of female reproduction, including the fecundity, ovaries, central nervous system (CNS), oocytes, embryos, oviducts, cytogenetics of somatic and generative cells, intracellular signaling systems, and hypothalamic, pituitary and peripheral reproductive hormones. Analysis of the available literature demonstrates that BTEX can exert negative effects on various female reproductive sites, including the CNS-pituitary-ovarian axis, their signaling molecules and receptors, ovarian follicles, *corpora lutea*, oocytes, embryos, oviducts, ovarian cycles, fertility, and the viability of offspring. These effects could be due to the ability of BTEX to destroy chromosomes, to affect cell metabolism, including the accumulation of free radicals, and to affect the release of hormonal regulators of reproductive processes and intracellular protein kinases.

Contents

1. Introduction

Oil production and processing and the subsequent production and consumption of petroleum products represent the basis of a modern economy. Unfortunately, leaks and spills of oil products (e.g., crude oil, petroleum, petrochemical products, aromatic hydrocarbons, etc.) are among the most common hazardous sources of environmental contamination. The petroleum low-weight aromatic hydrocarbons benzene, toluene, ethylbenzene, m/p-xylene, and o-xylene, also known as 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, etc.), (2) relatively high solubility in water and air and therefore easy migration and distribution in the environment and easy

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transport into the cells, (3) low physico-chemical and biological degradation in ecosystems, and (4) multiple toxic influences on living organisms [1].

BTEX can express toxic [2,1,3–6], mutagenic [7,8], carcinogenic [2,8], embryotoxic and teratogenic [9–12], growth retarding [13,9,4,14,11], metabolic [4,14], and neuromodulatory [15–18,8,19] effects.

The most dangerous effects of BTEX could be their influence on the most important biological process – reproduction, especially female reproduction and its regulators [20]. Female organisms accumulate 3.7–6.8 times more xylene than males, and ovaries are the primary accumulation site of these hydrocarbons [44]. The developing fetus is particularly sensitive to BTEX action [12].

1.1. Effects of BTEX on the ovarian morphology and fecundity

Female workers' contact with **benzene** is associated with ovarian hypo- and hyperplasia, ovarian and uterine retardation [2], reduction in the duration of the luteal phase of the menstrual cycle [21,22], and the retardation of fetal growth during pregnancy [11,12]. Increase benzene concentration in human ovarian follicular fluid was associated with reduced oocyte and embryo production, although pregnancy rate was not linked with ovarian benzene level [23]. Exposure of mice to benzene increased the incidence of ovarian granulosa cell tumors and ovarian benign mixed tumors [24]. Exposure of cows to benzene increases the incidence of odd calves [10]. **Toluene** exposure in rats suppresses the development of growing but not primordial ovarian follicles [25]. The inhalation of toluene increases the incidence of maternal and fetal morbidity and embryonic malformations in women [26,5], cows [10], and rats [14], although other studies have not detected any adverse effects on implantation or the number and viability of rat fetuses. Inhalation of **ethylbenzene** does not affect rat ovarian structure, function, and fertility [3]. The accessible databases do not contain publications concerning the reproductive effects of **xylenes,** although decreased embryonic growth [13] and increased prenatal mortality [9] in rats exposed to xylene have been reported.

Although extra- and intracellular mechanisms of BTEX action could help to explain and prevent their negative effects on reproduction, they have been very poorly studied. There is some evidence that BTEX can affect reproduction and fertility via several, most likely interrelated, mechanisms and target sites: via toxic and genomic effects on the CNS, hypothalamic, pituitary and peripheral hormones, reproductive organs, oocytes, and embryos.

1.2. Effects of BTEX on the CNS

The inhibitory effects of **benzene** [8], **toluene** [15,17–19,27], and **ethylbenzene** [16,19] on neuromediator receptors in the CNS are well known. In addition, toluene was able to exert its neurotoxic effect via an increase in brain free radicals [17]. Neuromediators play a key role in the control of sexual behavior and of neuromediator-dependent neurohormones, including gonadotropin-releasing hormones, oxytocin, etc., which in turn are the main regulators of the downstream pituitary-ovarian axis [28].

1.3. Effects of BTEX on hypothalamic, pituitary, and peripheral reproductive hormones

Women with occupational exposures to various BTEX (**benzene, ethylbenzene, toluene, and xylenes**) have reduced preovulatory blood gonadotropin (follicle-stimulating hormone, FSH, luteinizing hormone, LH) and prostaglandin level [22,29]. High **benzene** level in woman ovarian follicular fluid was associated with increased FSH and decreased estradiol level in blood plasma [23]. The inhalation of **toluene** by rats reduces the hypothalamic level of GnRH and plasma levels of gonadotropins, changes the FSH:LH rate, and increases the plasma level of anti-gonadotropin prolactin. These changes are associated with reduced blood progesterone and estradiol levels but not with their response to gonadotropin administration [30]. Inhalation of para-**xylene** decreases plasma progesterone and estradiol levels but not the release of these hormones by ovaries in rats [13]. These observations suggest that BTEX can reduce the output of ovarian steroid hormones via the inhibition of upstream hypothalamic gonadotropin-releasing hormone (GnRH)/pituitary gonadotropin production or the response of the ovary to gonadotropin.

1.4. Effects of BTEX on oocytes

Xenopus oocytes are used as a common model for studying the effects of BTEX on membrane receptors. These oocytes demonstrate inhibitory effects of **benzene, m-xylene,** and **ethylbenzene** on membrane N-methyl-D-aspartate (NMDA) receptors [16]; of **benzene** on gamma-aminobutyric acid (GABA) receptors [15]; of **toluene** on nicotinic acetylcholine receptors [18,27] and ethanol-sensitive potassium channels [31]; and of **xylenes** on nicotinic acetylcholine receptors [32]. Therefore, BTEX might also suppress reproduction via the inhibition of oocyte signaling systems.

1.5. Effects of BTEX on embryos

BTEX can disrupt reproduction due to their embryotoxic and teratogenic actions. The suppressive effects of **benzene, m-xylene, ethylbenzene, and xylenes** on bovine [10] and human [9,11,33] embryogenesis and of **toluene** [34] and **xylene** [9] on rat embryonic growth have been reported. In addition, toluene is able to inhibit steroidogenic enzymes and testosterone synthesis in fetal rats [35], suggesting the potential inhibitory influence of this aromatic hydrocarbon on gonadal steroidogenesis and related sexual maturation. There are some evidence for critical windows of vulnerability during prenatal and early postnatal development, during which BTEX exposures can cause potentially permanent damage to the growing embryo and fetus [12]..

1.6. Effects of BTEX on oviducts

Fertility and embryo viability could be influenced by BTEX via an influence of oviduct and uterine functions. Riveles et al. [36] reported that **benzene** exposure inhibits ciliary beat frequency, oocyte pickup rates, and infundibular smooth muscle contraction rates. The inhalation of para-**xylene** does not influence rat uterine and ovarian venous outflow [13].

1.7. Effects of BTEX on cytogenetics of somatic and generative cells

Cytogenetic analysis demonstrated the mutagenic effects of **toluene** and its analogues on hamster ovarian cells [7]. **Benzene** increased the incidence of aneuploidy in mature mouse oocytes [37]. The destructive effects of BTEX on chromosomes in somatic ovarian, brain, and other cells and in oocytes could be due to the ability of BTEX to increase the level of mutagenic and pro-apoptotic free radicals in these cells. The inhalation of toluene increased the activities of glutathione peroxidase and catalase and the intensity of lipid peroxidation in rat ovaries and brain cortices [17].

1.8. Effects of BTEX on intracellular signaling systems

The ability of BTEX to inhibit growth and induce cell death suggests that these hydrocarbons can suppress cell proliferation and promote cell apoptosis. Nevertheless, there is only