

The Possible Toxic Effect of 4-tert-octylphenol-Polluted Water, on Male Reproductive Hormone of Rat

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Abstract: Background: Many phenolic xenoestrogens have been reported to have mimic estrogen effects, and may adversely affect the health and reproduction of animals and human. The aim of this study was to estimate the concentration of 4-tert-octylphenol (OP), as example of xenoestrogens, in different areas and seasons of Ismailia Canal and to evaluate the activity of OP on reproductive functions of male albino rats. **Method:** water was collected from the different five tested areas among the four seasons of the year of Ismailia Canal then the concentration of OP was determined by GC in each area. To estimate the possible toxic effect of octylphenol on male reproductive hormones of rat, adult male albino rats were treated with low dose (10 μ g/kg/day) and high dose (450 mg/kg/day) of OP by oral administration for 4 weeks. The levels of prolactin, follicle stimulated hormone (FSH), Luteinizing hormone (LH) and testosterone were determined in rat serum. The **results** of this study indicated that water OP concentrations at all 5 chosen areas of Ismailia canal among the 4 season of the year (winter, spring, summer and autumn) were highly increased (>35fold) in comparison to the values obtained from metallic drinking water (aqua water 0.04 μ g.L⁻¹). The data also indicated that the highly polluted area by OP was in the area of oil companies and detergent factor, that showed maximum concentration (2.5 μ g.L⁻¹) in the level of OP in the summer season followed by Aboza`abal area (1.9 μ g.L⁻¹) in the spring season. The administration of OP resulted in a significant elevation in serum prolactin and FSH levels. On the other hand, there was a significant decline in serum LH and testosterone levels, after administration of both low and high doses. The obtained data also revealed a significant decrease in sperm count in all treated groups and this confirmed by the histopathological study. **In conclusion:** the findings of the present study raise the possibility that consumption of OP in drinking water may adversely influence male reproductive hormones and in turn its fertility.

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INTRODUCTION

The River Nile is subjected to pollution in some areas from wastewater of industry or agriculture origin. This pollution is limited compared with that in other canals such as Ismailia Canal. Ismailia Canal is considered highly polluted because of the presence of many factories which drain their industrial wastewater into the canal (Tarek and Osama 2007). Discharging of petroleum and petroleum derivatives industrial wastewater to Ismailia Canal pollutes the canal water with hydrocarbons, polyaromatic hydrocarbons, alkanes (PHA) and aromatic hydrocarbons. These are hazardous, toxic and carcinogenic compounds that are present due to petroleum fractionation (Tarek 2007). In recent years concern has been raised about the possibility that reproductive disorders reported in humans and

wildlife populations might stem from exposure to substances present in the environment which mimic estradiol, the so-called xenoestrogens, among them, 4-tert-octylphenol (OP), 4-nonphenol and bisphenol A, were studied in various researches. Exposure to chemicals with estrogenic activity may have potential to adversely affect the endocrine system and reproductive organs in males and females (Hejmej et al., 2011). Alkylphenols and their metabolites are lipophilic substances exerting apparent estrogenic action in vitro and in vivo testing systems. With the widespread industrial use of alkylphenols, these are disseminated in the environment with sewage sludge. There is evidence showing that alkylphenols can accumulate in vivo, at least in fish. Domestic animals and human are likely to be exposed via the food chain (Bian et al. 2006). 4-tert-octylphenol accumulation

was observed in liver, muscle and plasma up to 12 h whereas in testis 18 h post administration (Madsen et al., 2006). Studies on the exposure of U.S. population to OP revealed that this compound was present in the urine of 57% of persons >6 years of age with total concentrations ranging from 0.2 g/L to 20.6 g/L (Calafat et al., 2008). Currently, OP has been also found in human breast milk (Ademollo et al., 2008).

4-tert-octylphenol can affect invertebrates, amphibians and fish, possibly by endocrine disrupters through an estrogen mediated mode of action, with some evidence of thyroidal activity in amphibians (ECETOC 2009, Evans et al., 2011)). There is some evidence that exposure of early life stages to low $\mu\text{g/L}$ concentrations results in developmental delays and changes in reproductive outcome (OECD, 2011). Octylphenol is an important intermediate in the production of a number of commercial materials. The major use of OP is for the production of alkylphenol ethoxylates (OPE), a class of nonionic surfactants with a wide range of applications (Pocar et al., 2003). Results published by Greenpeace (2011) indicate that octylphenols might be used in China in textiles for the European market showing that octylphenols were found in nearly all analyzed imported colored textile articles. Exposure to OP is a matter of concern because it has been shown to be both estrogenic and toxic to mammalian cells (Blake et al. 2004, Antonia et al., 2008), thus the removal of OPE and their metabolites during wastewater treatment, applying conventional activated sludge treatment and membrane bioreactors, was in concern in the recent studies (Mira and Damià 2010).

The aim of this work was to detect OP in Ismailia Canal which is one of the drinking water sources in Egypt and highly polluted with the industrial waste and to investigate the effect of OP, as an estrogenic mimic, on the reproductive hormones in adult male rats.

MATERIALS AND METHODS

Detection of OP in Ismailia Canal

Sample Collection: Five water samples will be collected along Ismailia canal water and the concentration of 4-tert-octylphenol will be determined, the sampling sites are:

- 1- At 8 kilometer from the beginning of Ismailia canal water (Inlet of Mostorod Drinking Water Treatment Plant).
- 2- At 10 kilometer from the beginning of Ismailia canal water (after oil companies and detergent factor).
- 3- At 27 kilometer from the beginning of Ismailia canal water (after AboZa'abal factory for fertilizer and chemicals manufacture).
- 4- At 65 kilometer from the beginning of Ismailia canal water (middle of the canal to study the effect of dilution).
- 5- At, outlet of Mostorod: Drinking water sample will be taken from the storage tank of Mostored, to study the efficiency of conventional treatment methods for removal of OP.

Extraction, derivatization and determination of OP by GC were done according to the method of Xinglong et al., (2004) and Riken, (2001) respectively.

Biological Study

Material: 4-tert-octylphenol standard was purchased from Sigma CO, USA. The substance was dissolved in corn oil and the concentration was adjusted to obtain two different doses, low dose; 10 $\mu\text{g/kg/day}$ (Bogh et al., 2001) and high dose; 450 mg/kg/day (Bian et al., 2006).

Animals: Adult Male albino rats weighing 100-120g were used. The animals were brought from laboratory animal breeding of National Organization for Drug Control and Research (NODCAR), Giza, Egypt. They were kept under strictly hygienic conditions, fed on a standard basal diet, and allowed free access to drinking water. Before the beginning of the experiment, rats were allowed to adapt to the environment for one week. The experimental protocols were approved by the NODCAR's Institutional Ethical Guidelines for Animal Care and Usage.

Experimental Design: Rats were classified into 3 equal groups each comprises 12 rats and treated daily for 4 weeks, as follow:

Group 1 (Positive control group): Rats fed on basal diet and received corn oil as vehicle.

Group 2 (Low dose treated-group): Rats were orally administered 10 $\mu\text{g/kg/day}$ of 4-tert-octylphenol once daily.

Group 3 (High dose treated–group): Rats were orally administered 450 mg/kg/day of 4-tert-octylphenol once daily.

After time intervals of 1, 2, 3 and 4 weeks, blood samples were withdrawn from rats of each group, collected, left to coagulate and serum was separated. The separated sera were processed for the biochemical analysis which included ELIZA techniques for: Prolactin assay according to method of Sinha (1995), FSH and LH methods, according to Levine et al., (1985) and testosterone concentration, according to Andreyko et al., (1986).

At the end of the treatment schedule, the animals were sacrificed and the testis were excised and collected for histopathological studies of Culling (1974). Also the sperms were collected from the seminal vesicles for sperm count (John 1982).

Statistical analysis: Data are expressed as mean \pm SE. All the data were analyzed using one way analysis of variance (ANOVA) followed by determination of least significant difference (LSD) for multiple comparison test. P-values \leq 0.05 were considered significant.

RESULTS

Water Analysis Results

The characteristic peak areas of the derivative analytics were selected and their concentrations were listed in table (1). The results showed that OP concentrations at all 5 chosen areas of Ismailia Canal among the 4 season (winter, spring, summer and autumn) of the year were very highly increased ($P < 0.005$, > 35 fold) in comparison to values obtained from metallic drinking water (Aqua water concentration = $0.04 \mu\text{g.L}^{-1}$). The data indicated that the area of oil and detergent at kilo 10 showed maximum concentration ($2.5 \mu\text{g.L}^{-1}$) in the level of OP in the summer season followed by Aboza`abal area ($1.95 \mu\text{g.L}^{-1}$) in the spring season. The arranged order of OP concentration in the different chosen areas (taking, the average value of the four seasons for each area) was; $1.95 \mu\text{g.L}^{-1}$ (kilo 10 at oil companies and detergent factor) $> 1.64 \mu\text{g.L}^{-1}$ (Kilo 27 at Aboza`abal) $> 1.44 \mu\text{g.L}^{-1}$ (kilo 8, inlet of Mostorod) $> 1.40 \mu\text{g.L}^{-1}$ (kilo 65, effect of dilution) $> 1.39 \mu\text{g/L}$ (outlet of Mostorod).

II-Hormonal Results

Serum FSH level

As shown in Fig (1) and table (2), the low dose revealed a significant increase ($P < 0.005$) in FSH

level only at 4th week of treatment in compared with the corresponding control. On the other hand, high dose of OP increased FSH level significantly ($P < 0.005$) from the second week until the end of duration, as compared with that of their corresponding controls. There was a significant difference between the two doses level, $P < 0.05$ especially through the third and fourth week, i.e. data exhibited a dose and time dependant manner.

2-Serum LH level

The level of LH showed very highly significant decrease ($P < 0.005$) throughout the all period of treatment with both doses as compared to control, Fig (2) and table (3). No significant difference could be detected between the effects of the two doses.

3-Serum testosterone level

The data in Fig (3) and table (4) reported that the level of testosterone showed very highly significant decrease ($P < 0.005$) during the all periods of treatment in all groups with low and high doses. In case of low dose treatment, the testosterone level through the 2nd, 3rd, and 4th week revealed significant decrease, $P < 0.05$. On the other hand the level in groups treated with high dose during 3rd, 4th week of treatment showed significant decrease as compared to the 1st week of treatment, $P < 0.05$.

4-Serum Prolactin level: As shown in Fig (4), and table (5), the low dose of OP significantly elevated the prolactin level starting from 2nd week of treatment until the end of experiment as compared with their corresponding control, $P < 0.005$. Also, the prolactin level showed significant increase in the 2nd, 3rd, and 4th week of treatment, as compared to that of the 1st week of treatment, $P < 0.05$. Regarding the high dose administration, there was a significant increase in prolactin level starting from 1st week of treatment when compared with corresponding control, $P < 0.005$. Prolactin level showed significant difference through the 3rd and 4th week of treatment, as compared to that of the 1st week of treatment, $P < 0.05$. No significant difference could be detected between the two doses through the 1st and 2nd week of treatment. While the level in 3rd, 4th week of treatment with high dose showed significant increase when compared with that of low dose, $P < 0.05$, i.e. data exhibited a dose and time dependant manner.

5-Sperm count:

As listed in table (5), there was a significant reduction ($P < 0.01$) in sperm count as compared with

control group. Data exhibited dose dependent manner.

Histopathological Results

Control group

Light microscopic examination of the testis of control albino rats revealed normal appearance of seminiferous tubule. Fig (6a)

Low dose group

Testis tissues of low-dose treated group revealed mild pathological changes in form of congested, dilated subcapsular blood vessels. Seminiferous

tubules showed normal staining and morphological character; however few showed spermatogenic arrest together with sertoli cell degeneration, Fig (6b).

High-dose group

Sever toxic effect shown, in high-dose-treated group, where thickened capsule with congested, dilated subcapsular blood vessels were present. Spermatogenic arrest was observed in the majority of the seminiferous tubules, with signs of atrophy in many of them, Fig (6c).

Table (1): Concentrations of OP ($\mu\text{g.L}^{-1}$) level in Ismailia Canal at different five areas among the four seasons of year.

Area Seasons	Aqua water (Control)	At kilo 8 (Mostorod inlet area)	At kilo10 (Oil& Detergent area)	At kilo 27 (Abo- za`abal area)	At kilo 65 (Dilution area)	Mostorod outlet area
Winter	0.04 \pm 0.003	1.45 \pm 0.056***	1.37 \pm 0.094***	1.70 \pm 0.041***	1.18 \pm 0.077***	1.27 \pm 0.084***
Spring		1.73 \pm 0.066***	1.61 \pm 0.046***	1.90 \pm 0.040***	1.60 \pm 0.050***	1.41 \pm 0.044***
Summer		1.33 \pm 0.054***	2.50 \pm 0.037***	1.47 \pm 0.091***	1.65 \pm 0.044***	1.60 \pm 0.084***
Autumn		1.23 \pm 0.060***	2.33 \pm 0.065***	1.43 \pm 0.088***	1.18 \pm 0.041***	1.21 \pm 0.060***
Average values		1.44 \pm 0.088*** 36.00 F	1.95 \pm 0.123*** 48.75 F	1.64 \pm 0.092*** 41.00 F	1.40 \pm 0.105*** 35.00 F	1.37 \pm 0.071*** 34.85 F

Data are expressed as the mean values of 6 samples \pm SE F= fold
Very highly Significant difference vs. control Aqua water: *** P<0.005

Table (2): The effect of low and high doses of 4-tert-octylphenol treatment on the level of serum FSH (mIU/ml) during time course of treatment.

Doses	1 st week	2 nd week	3 rd week	4 th week
Positive Control	0.87 \pm 0.070	0.85 \pm 0.067	0.87 \pm 0.074	0.84 \pm 0.090
Low Dose (10 $\mu\text{g/kg/day}$)	0.98 \pm 0.10 ↑	1.0 \pm 0.21 ↑	1.09 \pm 0.94 ↑	3.87 \pm 0.86 ***↑
High Dose (450mg/kg/day)	0.96 \pm 0.065 ↑	1.30 \pm 0.11 *↑	2.34 \pm 0.32 ***↑	6.60 \pm 0.31 ***↑

Data expressed as mean \pm SE for 12 rats, *P <0.05 significantly different from control.
*** P<0.005 very highly significantly different from control.

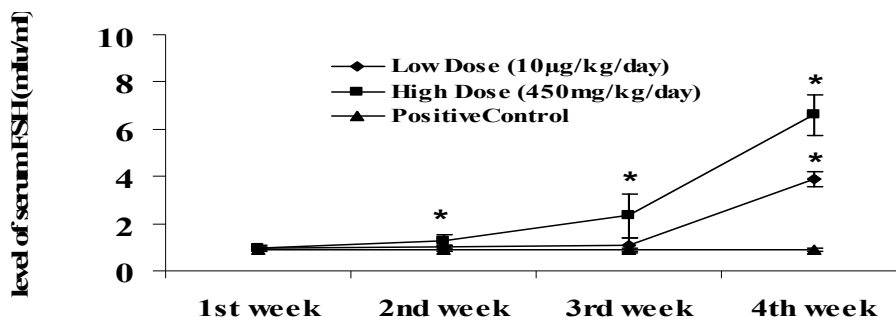


Fig (1): The effect of time course (4weeks) on serum FSH levels by 4-tert-octylphenol treatment -Significant different vs. 1st week: *P<0.05.

Table (3): The effect of low and high doses of 4-tert-octylphenol treatment on the Level of serum LH (mIU/ml) during time course of treatment.

Doses	1 st week	2 nd week	3 rd week	4 th week
Positive Control	0.40 ± 0.048	0.39 ± 0.046	0.42 ± 0.048	0.41 ± 0.050
Low Dose (10 µg/kg/day)	0.15 ± 0.025 **↓	0.099 ± 0.024 ***↓	0.084 ± 0.028 ***↓	0.067 ± 0.028 ***↓
High Dose (450 mg/kg/day)	0.20 ± 0.012 *↓	0.083 ± 0.014 ***↓	0.073 ± 0.008 ***↓	0.019 ± 0.010 ***↓

Data expressed as mean ± SE for 12 rats, *P < 0.05, ** P < 0.01 and *** P < 0.005: significantly, highly significantly and very highly significantly different from control.

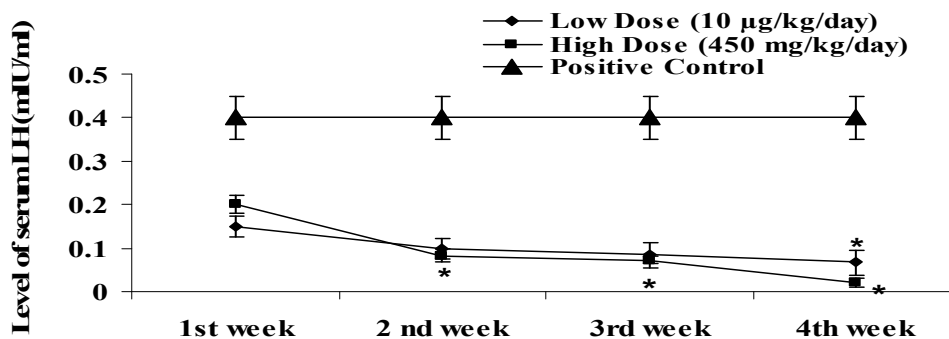


Fig (2): The effect of time course (4weeks) on serum LH levels by 4-tert-octylphenol treatment -Significant different vs. 1st week: *P<0.05.

Table (4): The effect of low and high doses of 4-tert-octylphenol treatment on the Level of serum testosterone (ng/ml) during time course of treatment

Doses	1 st week	2 nd week	3 rd week	4 th week
Positive Control	2.52 ± 0.20	2.50 ± 0.22	2.51 ± 0.23	2.47 ± 0.20
Low Dose (10 µg/kg/day)	1.11 ± 0.036 *↓	0.50 ± 0.070 ***↓	0.44 ± 0.086 ***↓	0.22 ± 0.050 ***↓
High Dose (450 mg/kg/day)	0.60 ± 0.11 ***↓	0.42 ± 0.090 ***↓	0.24 ± 0.030 ***↓	0.15 ± 0.022 ***↓

Data expressed as mean ± SD for 12 rats, *P < 0.05, *** P < 0.005: significantly and very highly significantly different from control.

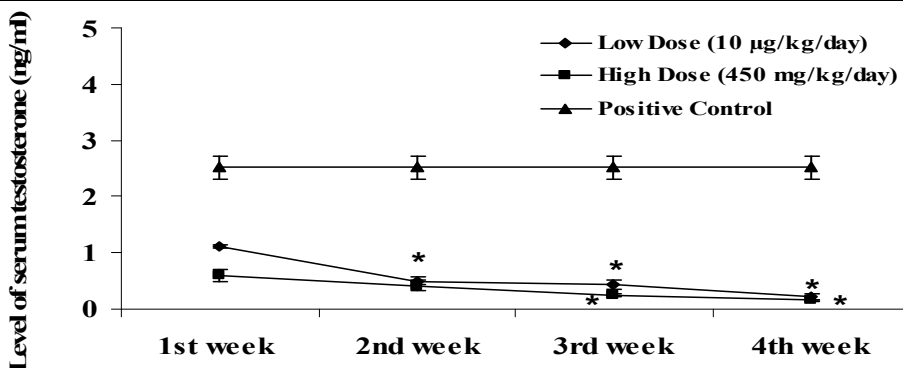


Fig (3): The effect of time course (4weeks) on serum testosterone levels by 4-tert-octylphenol treatment
 - Significant different vs. 1st week: *P<0.05.

Table (5): The effect of low and high doses of 4-tert-octylphenol treatment on the Level of serum prolactin (ng/ml) during time course of treatment

Doses	1 st week	2 nd week	3 rd week	4 th week
Positive Control	0.43 ± 0.020	0.41 ± 0.22	0.43 ± 0.017	0.42 ± 0.021
Low Dose (10 µg/kg/day)	0.56 ± 0.036 ↑	0.82 ± 0.060 *** ↑	0.77 ± 0.077 *** ↑	0.85 ± 0.076 *** ↑
High Dose (450 mg/kg/day)	1.12 ± 0.28 ***↑	1.68 ± 0.54 ***↑	2.77 ± 0.56 *** ↑	3.7 ± 0.44 *** ↑

Data expressed as mean ± SE for 12 rats, *** P<0.005 very highly significantly different from control

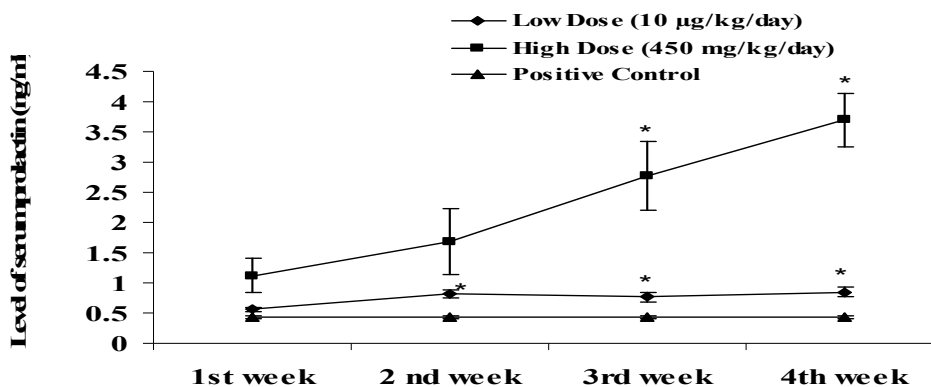


Fig (4): The effect of time course (4weeks) on serum prolactin levels by 4-tert-octylphenol treatment
 - Significant different vs. 1st week: *P<0.05.

Table (6): The effect of low and high doses of 4-tert-octylphenol treatment on the sperm count variations after 4 weeks of treatment

Positive control	Low Dose (10 µg/kg/day)	High Dose (450 mg/kg/day)
113.33 ± 22.70	55.16 ± 10.20 ↓**	39.00 ± 3.57 ↓***

Data expressed as mean ± SD for 12 rats, ** P < 0.01 highly significantly, *** P<0.005 very highly significantly different from control.

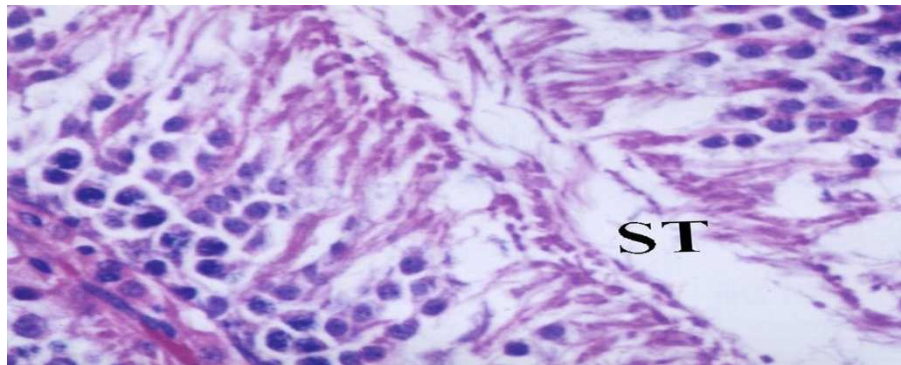


Fig (6a): A photomicrograph of testis tissue, demonstrating intact seminiferous tubule (ST) with normal spermatogenesis, H&E, X: 400

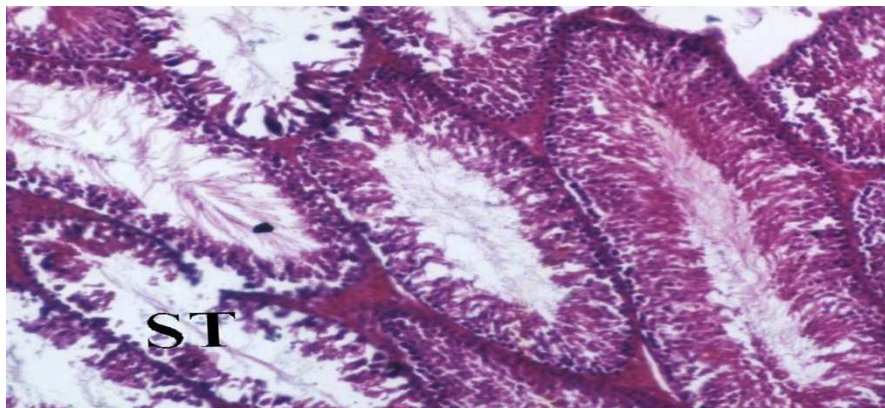


Fig (6b): A photomicrograph of testis tissue of low dose-treated group, showing spermatogenic arrest in few of somniferous tubule (ST) H&E, X: 400

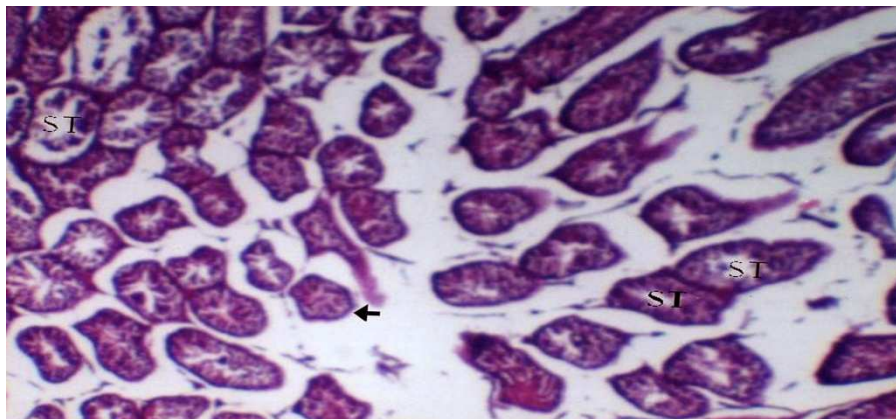


Fig (6 c): A photomicrograph of testis tissue, of high dose-treated group of rats, showing many atrophied somniferous tubule (arrow), some showed spermatogenic arrest (ST). H&E, X: 400

DISCUSSION

The average levels of 4-tert-octylphenol especially at first 10 km of the Ismailia Canal related to its wide spread in the environment and due to the numerous

contaminated sources at this region, presence of a lot of industrial factories such as paper, food, petroleum and petroleum derivatives industries that discharge their wastewater without treatment to Ismailia Canal

water. These intern pollutes the canal water with hydrocarbons, PAH, alkanes and aromatic hydrocarbons (Tarek 2007). In Germany, four municipal wastewater treatment plants reported emissions of octylphenol and octylphenol ethoxylates in a range from 4.31 to 17.6 kg. The maximum release reported by a single producer of industrial chemicals remains at 175 kg (BAuA 2011). Thus, the expected emission in Egypt may be more in Ismailia Canal (35F increase than the normal aqua water) and in turn maximum pollution and side adverse were occurred. 4-tert-octylphenol is used as precursor in the manufacture of textile, non ionic surfactants and is also degradation products of alkylphenol ethoxylate, which are used in household detergents, pesticide formulations and others applications (Renner 1997, Greenpeace 2011), thus 4-tert-octylphenol was considered as an environmental contaminant, has been reported to induce reproductive abnormalities in male rats. Injection of OP to adult male rats has devastating effects on their reproductive system (Bian et al., 2006). The results of the present study revealed that oral administration of OP at 10 µg/kg and 450 mg/kg of 4-tert-octylphenol once daily for 4 weeks, can seriously alter the male reproductive system and this effect was more serious with the high dose. 4-tert-octylphenol may cause endocrine mediated effects in a variety of species. in Fisher rat, all 4-tert-octylphenol treated groups (20, 40, 80 mg/kg bw) showed decreased in terminal body weights, epididymis and seminal vesicle weight, serum testosterone concentrations as well as histopathological changes in testes (with reduction in number of germ cells) and increase in LH serum concentrations (Kim et al., 2004). In contrast, the study of Sahambi et al., (2010) on female adult rats showed no effect on uterine & ovarian histopathology and serum estradiol unaffected by OP treatment. Also, Gregory et al., (2009) revealed no effect on histopathology or organ weights of reproductive organs of adult male rats and epididymal sperm count Unaffected. On the other hand oral dose variance effect by OP was studied by Bian. et al., (2006), they showed that at daily doses of approximately 150 mg/kg bw of 4-tert-octylphenol to juvenile/adult male rats did not reveal any morphological abnormalities in testes and germinal epithelium. Whereas, when administered at high doses (≥ 400 mg/kg bw/d) they revealed systemic effects such as reduced body

weight gain, adverse effects were revealed also for male reproductive organs (decreased organ weights of testes, epididymis and prostate, morphological defects in testes), testicular sperm (reduced sperm count) and increase serum prolactin levels. These aforementioned results are in consistent with the present study that showed obvious histopathological changes in testes and marked reduction in number of sperm count with the high dose (450 mg/kg). On the other hand, studies using subcutaneous injection (s.c), doses of ≥ 20 mg/kg/B.wt revealed histopathological changes in testes (with reductions in number of germ cells and in testicular sperm count, changes in sperm morphology), decreases in epididymal and in seminal vesicle organ weight, and decreases in serum testosterone and increases in serum LH levels, a pattern of effects identical to that seen with concomitant s.c. administration of the estrogen 17 β -estradiol. (BAuA 2011)

Overall there are conflicting results with regard to 4-tert-octylphenol interfering with the male reproductive system that, significantly dependent on the species, dose and route of administration.

The results of the present study revealed that OP induced a significant elevation in the FSH level and concomitant decrease in the LH level at low and high doses studied, Fig (1 & 2). Neil et al., (2003) suggested that the differences in the response of FSH and LH to Bisphenol-A (an example of xenoestrogens) might be due to differential sensitivity of the systems regulating FSH and LH secretion to OP at the level of the pituitary or the hypothalamus. In concomitantly, other authors reported that Bisphenol-A could have hypothalamic actions (Funbashi et al., 2003). So that OP can alter levels of progesterone receptor expression within the mediobasal hypothalamus. These induced changes in neural systems that could impact upon FSH and LH release. Sweeny et al., (2000) demonstrated that differences in the ability of Bisphenol-A to alter FSH and LH release might be related to differences in the number of distribution of estrogen receptor subtypes α , β and γ . These receptors exhibit different binding affinities for specific disruptors and can achieve differential effects through different estrogen responsive elements.

One of the most critical estrogenic influences that OP may have effect on the reproductive system is to induce a decrease in testosterone secretion (Boockfor

et al., 1997; Kim et al., 2007). The results of the present work revealed that there was a decrease in the testosterone level. This is in agreement with results of Akingbemi et al., (2003). The author reported that xenoestrogens has adverse effects on testicular function by decreasing pituitary LH release and reducing Leydig cells steroidogenesis, so OP suppresses testosterone production through decreased LH secretion. There is an evidence that xenoestrogen interferes with LH receptor-ligand binding (Akingbemi et al., 2003). In addition, a study on ICR mice, effects of 4-tert-octylphenol on the expression of steroidogenic enzymes and on testosterone production were investigated, it was shown that juvenile exposure to 4-tert-octylphenol inhibits steroidogenesis by decreasing the expression of steroidogenic enzymes in the testis, hence resulting in decreased testosterone synthesis. Diminished lipid content in Leydig cells together with reduced transcriptional expression of the cholesterol transport gene, also support altered cholesterol metabolism and/or transport as a potential mechanism for decreased testosterone production following exposure to 4-tert-octylphenol.

In this work, the increase in serum prolactin is in agreement with a study conducted by Blake and Boockfor (1997). The author hypothesized that OP might act qualitatively like estrogen in vivo to suppress gonadotropin and testosterone secretion and enhances prolactin secretion. Similar results were obtained by Rosenmary et al., (1997). The author mentioned that Bisphenol-A which with estrogen like effect mimicked estradiol in induction of hyperprolactinemia in an estrogen-sensitive rat. Arnold et al., (1996) mentioned that the combination of two xenoestrogens (OP and estradiol benzoate) might be higher in activating estrogenic receptors than each compound alone. Furthermore, Kuiper et al., (1998) suggested that xenoestrogen can induce hyperprolactinemia by altering estrogen receptor and/or estrogen-responsive genes that affect lactotrophs in rats.

The marked reduction of sperm count produced in the present study by high dose (450mg/kg) of OP was in consistent with the study of Bian et al. (2006), they reported a decrease in germ cell number, a decrease in the seminiferous tubules of the testis, decreased tubule size, and a disruption of normal spermatogenic cell organization were found in the highest dose

group (400mg/kg). In addition, rats from this group displayed significant decrease in daily sperm production. Many studies investigated the effect of 4-tert-octylphenol spermatogenesis through an SGP-2 dependent mechanism effects on the expression of Sulphated Glycoprotein-2 (SGP-2) mRNA, a biomarker for spermatogenesis in Sertoli cells of rat testes (Yon et al., 2007). or via abnormal enhancement of phospholipid hydroxyl-peroxidase glutathione peroxidase expression in testes, an antioxidative selenoprotein, which interacts directly with peroxidised phospholipid, cholesterol and cholesteryl esters (Baek et al., (2007), or affects Leydig cells via impairment of 3 β -hydroxysteroid dehydrogenase/lyase, a key enzyme in steroidogenesis and molecular marker for androgen biosynthesis (Kim et al., 2007).

In summary, OP when administered orally to male albino rats at 10 μ g/Kg and 450 mg/Kg for 4 weeks increased serum prolactin and FSH levels decreased LH and testosterone levels as well as histopathological changes in testes and reduction in sperm count were occurred. Thus, OP influences its reproductive hormones and in turns its fertility.

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