



TOXOPATHOLOGICAL STUDIES ON THE EFFECT OF HEAVY METALS EMITTED FROM SUPERPHOSPHATE FACTORY ON THE REPRODUCTIVE PERFORMANCE OF MALE GOATS

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ABSTRACT:

The present study was designed to evaluate toxopathological effects of heavy metals emitted from superphosphate factory on the reproductive performance of male goats. Thirty male goats were selected from Gaz. El-Akrad area adjacent to the factory (group 1) and five male goats from Dairut area (group 2) served as control. Serum samples were used for determination of cadmium, fluorine, testosterone and prostatic acid phosphatase. Tissue specimens were obtained from testes, epididymis and prostate for histopathological examination. It was observed that the level of cadmium and fluorine was significantly increased in the serum of exposed group when compared with control group. It was observed that the mean level of testosterone in group 1 was extremely significantly decreased while the level of prostatic acid phosphatase was significantly increased when compared with control group. Histopathological findings in the testicle of male goat of the group 1 revealed testicular degeneration with formation of spermatid giant cells. Congestion of the blood vessel, edema and fibrosis of the interstitial tissue with formation of sperm granuloma were noticed. The epididymis showed edema, fibrosis and necrosis of the epididymal tubules. The prostate gland showed edema, fibrosis and hyperplasia. Our results strongly suggest that cadmium and fluorine intoxication produces adverse effects on sexual fertility with hormonal and pathological alterations in male goats.

INTRODUCTION:

Industrial pollution is considered one of the most important problems in the whole world; it may lead to sever dangerous effects on biological systems. Manqabad superphosphate factory in Assiut governorate, Egypt emitted wastes such as cadmium (Cd) and fluoride which pollutes the areas around the factory during the process of manufacturing the

fertilizer (Sayed, 2001). Cadmium is a heavy metal and a major environmental toxicant. The general population is exposed to Cd via contaminants found in drinking water and food (WHO, 2000 and ATSDR, 2008). The common sources of fluorine poisoning are forage, pasture, water, feed supplement, mineral mixture and vegetation grown in soil containing exceedingly high levels of fluorine (Jagadish *et al.*, 1998).

Acute cadmium toxicity induced testicular damage is found at interstitial and tubular levels; permeability changes in the capillary endothelium, which derive in edemas, hemorrhages or necrosis, seem to be clearly implicated in the histopathological mechanism of these lesions (Biswas *et al.*, 2001; Laskey *et al.*, 1984). It is well known that long-term cadmium exposure has carcinogenic effects on the male reproductive organ (Koyama *et al.*, 2002; Waalkes, 2003) and causes a diminution of reproductive capacities (Saygi *et al.*, 1991 and Selypes *et al.*, 1992).

In male rodents, it is well established that Cd significantly alters the circulating levels of several hormones such as; testosterone, LH and FSH (Lafuente *et al.*, 2004). Previous studies have shown that Cd impairs the testosterone production in isolated Leydig cells without affecting their viability (Laskey and Phelps, 1991). Cd-induced cellular toxicity in the testis and may cause an increase in oxidative stress by binding to sulfhydryl groups of proteins and by depleting glutathione (Valko *et al.*, 2005). Thereafter, the oxidative stress may promote alteration of DNA repair mechanisms and induction of cell proliferation which in turn may lead to tumorigenesis (Beyersmann and Hartwig, 2008).

Prolonged exposure to fluoride damages the male reproductive organs, particularly the spermatogenic cells (Susheela and Kumar, 1991). Narayana and Chinoy, (1994) reported reduced sperm acrosomal hyaluronidase and acrosin, an increase in acrosomal damage, a

decline in sperm motility and decrease in cauda epididymal sperm counts in rats receiving sodium fluoride 10 mg/Kg body weight for 50 days by gavages. High doses of fluorine gas and hydrogen fluoride in animal studies have resulted in testicular degeneration. The available animal and human data strongly suggest that the reproductive system is a target of fluoride toxicity at high exposure levels (Robert Kapp, 2005).

The aim of the present study is to evaluate the toxopathological effect of heavy metals emitted from superphosphate factory on the reproductive performance of male goats.

MATERIALS AND METHODS:

The areas of study:

(A) Gaz. El-Akrad: This is a rural area from 0 Km to 2 Km south of superphosphate factory and in the wind direction. It was considered as group 1.

(B) Dairut area: This area located at 60 Km north of superphosphate factory. This area was taken as a control area. It was considered as group 2 (control group).

Samples:

Animals: Thirty male goats aged from 18-30 month were selected from Gaz. El-Akrad area and five male goats from Dairut area also aged from 18-30 month. The samples were collected through one month (October 2010). Whole blood samples were obtained from jugular vein of the studied animal during slaughtering.

Serum were collected after centrifugation of the blood samples at 3000 r.p.m for 10 minutes and stored at -20°C. Tissue specimens from testes, epididymis and prostate were taken and fixed in 10% neutral buffered formalin for histopathological examination.

Determination of cadmium and fluorine in serum:

Serum samples were digested according to Koirtyohann *et al.*, (1982) using nitric acid. All chemicals used were of analytical-reagent grade and the highest purity available. Double distilled deionized water, HPLC-grade, were used throughout. Glass vessels were cleaned by soaking in acidified solutions of nitric acid and rinsed several times with high-purity deionized water. Nitric acid (approx. 65%, Merck) was used. Metal levels were calculated on the basis of similarly prepared Merck standards. Cd and fluorine concentrations were determined in digested samples using Atomic Absorption Spectrophotometry (Atomic absorption 906, GBC, Australia). The analysis was done in Analytical Chemistry Unit (ACAL), Faculty of Science, Assiut University.

Determination of serum testosterone:

Testosterone hormone measured by quantitative enzyme immunoassay using commercially formulated kits (Biocheck, Inc. Foster City, CA 94404). The enzymes were detected by color and the absorbance was measured at 450 nm by ELIZA reader.

Determination of serum prostatic acid phosphatase (PAP):

PAP levels in serum were determined by calorimetric methods (Kind and King, 1954).

Histopathological Examination:

Specimens from testicles, epididymis and prostate were fixed in 10% neutral buffered formalin, dehydrated in a graded alcohol series, cleared with methyl benzoate and embedded in paraffin wax. Sections of 5 µm were cut and stained with haematoxylin and eosin (Bancroft *et al.*, 1996). Stained sections were examined under light microscope (Olympus CX31, Japan) and photographed using digital camera (Olympus, Camedia C-5060, Japan).

Statistical analysis:

Statistical analysis was carried out by analysis of variance (ANOVA) and the results were compared using student t test. All statistical tests were performed using Graph pad Software Package (Graph pad software, Inc, San Diego CA. USA).

RESULTS:

Determination of cadmium and fluorine in serum:

Estimation of cadmium and fluorine in serum was presented in Table (1). The levels of cadmium in serum of exposed male goats (group 1) were significantly increased when compared with control group. The levels of fluorine in serum of exposed male goats (group 1) were very significantly increased with the comparison of control group.

Table 1 : Serum levels of cadmium (mg/l) and fluorine (mg/l) in male goats in group 1 in comparison with control group

Groups	Cadmium (mg/l)	Fluorine (mg/l)
Group (1)	0.25±0.06*	0.12±0.01**
Group (2)	0.018±0.003	0.05±0.005

All values are expressed as mean ± SE

*Significant (P= 0.01 to 0.05).

**Very significant (P= 0.001 to 0.01).

Determination of testosterone and prostatic acid phosphatase:

In male goats, it was observed that the mean level of testosterone in group 1 was extremely significantly decreased (P<0.001) when compared with control group. The PAP in group 1 was extremely significantly increased (P<0.001) when compared with control group (Table 2).

Table 2: Serum levels of testosterone (ng/ml) and PAP (u/l) in male goats in group 1 in comparison with control group.

Groups	Testosterone (ng/ml)	PAP(u/l)
Group (1)	1.34±0.2	11.43±1.18 ***
Group (2)	3.54±0.3***	5.11±0.36

All values are expressed as mean ± SE

*** Extremely significant (P < 0.001)

Histopathology:

The incidence of the most common lesions in different groups was summarized in Table (3). Histopathological examination of HE-stained sections of the exposed group revealed degenerative changes within the seminiferous tubules. Much of the lining cells of the seminiferous tubules were sloughed

accompanied with characteristic multinucleated spermatid giant cells in the lumen. (Figs. 1 A, B). Congestion of the blood vessels and interstitial edema with proliferation of fibrous connective tissue was observed. Destruction of the basement membranes with escape of spermatogenic cells and lymphocytic infiltration in the interstitial tissue was also noticed (Figs. 1C,D). Moreover, spermatogenic granulomas were developed in some cases. These granulomas consisted of dead sperms, lymphocytes and fibroblast cells (Figs. 1E,F).

Examination of the epididymis revealed peritubular edema and fibrosis (Fig. 2 A). The lining epithelium of the epididymal tubules showed necrosis. The epididymal tubules appeared free of sperms (Fig. 2 B). The lesions in the prostate glands were expressed by interstitial edema and fibrosis. Hyperplasia of the epithelial lining and cystic dilatation in some parts were also noticed (Figs. 2 C-E).

Table 3: The incidence of the most common lesions in exposed group (1) and control group (2)

Lesion	G(1) (n=30)	G(2) (n=5)
Testicular lesions:		
Congestion of the blood vessels	30	0
Interstitial edema	30	0
Degeneration of seminiferous tubules	30	0
Presence of spermatid giant cells	30	0
Spermatogenic granuloma	4	0
Interstitial fibrosis	25	0
Epididymal lesions:		
Interstitial edema	30	0
Fibrosis	26	0
Necrosis of the epithelium	20	0
Prostatic gland lesions:		
Interstitial edema	30	0
Fibrosis	18	0
Hyperplasia of the epithelium	5	0

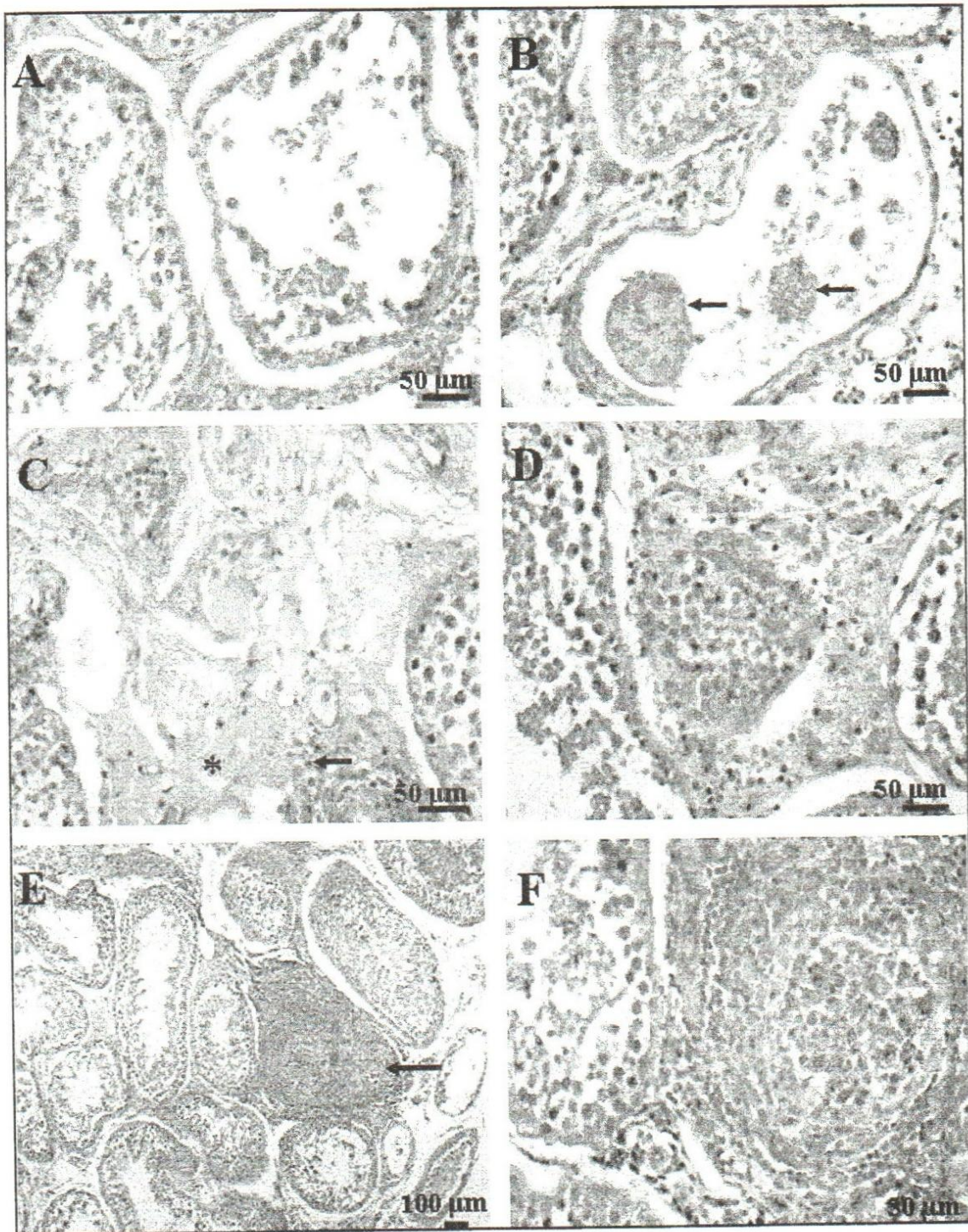


Fig. 1: Representative micrographs for histopathological findings in the testicle of male goat of the exposed group. A,B) Testicular degeneration with formation of spermatid giant cells (arrows). C) Congestion of the blood vessel, edema of the interstitial tissue (asterisk) associated with escape of spermatogenic cells (arrow). D) Edema and proliferation of fibrous tissue in the interstitium. E,F) Spermatid granuloma (arrow). H & E stain.

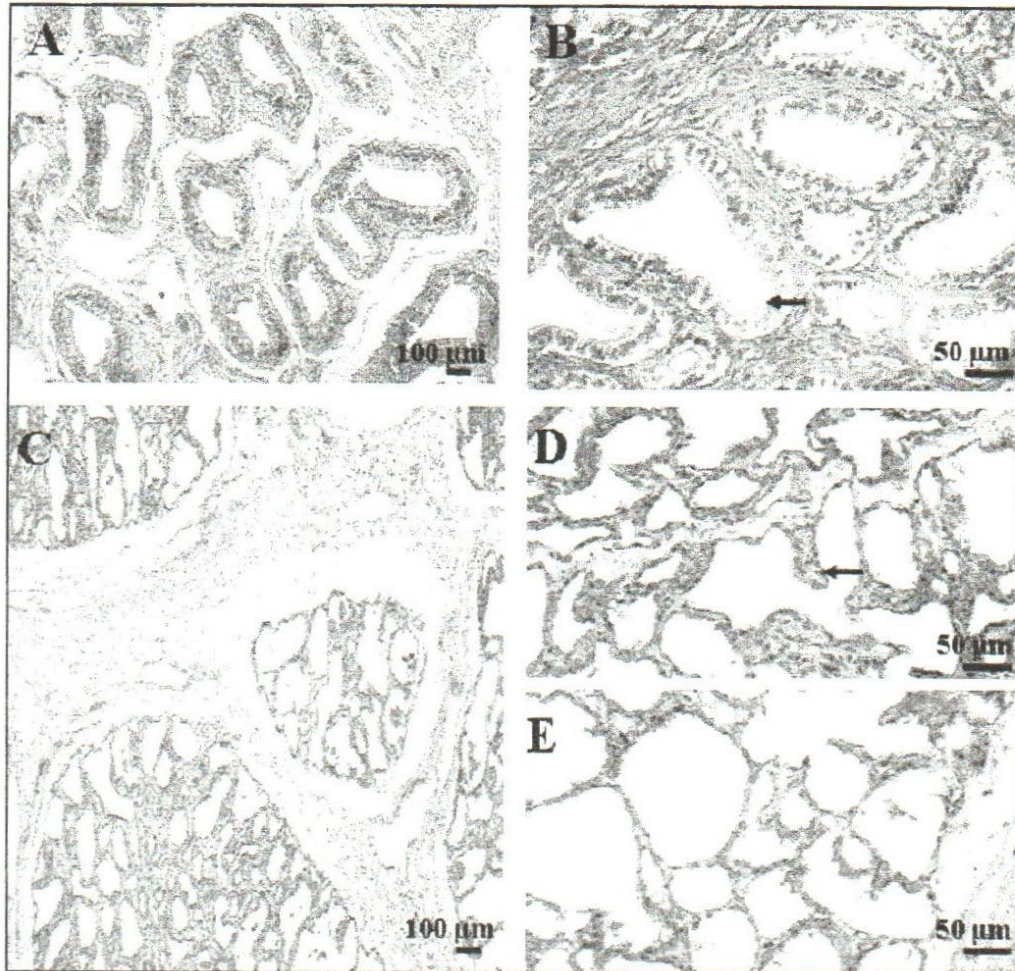


Fig. 2: Representative micrographs for histopathological findings in the epididymis and prostate of male goat of the exposed group. A) Epididymis showing edema and fibrosis. B) Necrosis of the epididymal tubules (arrow). C) Prostate gland showing edema and fibrosis. D) Higher magnification showing hyperplasia (arrow). E) Cystic dilatation in some parts of the prostate. H & E stain.

DISCUSSION:

Manqabad superphosphate factory in Assiut governorate, Egypt emitted wastes such as cadmium and fluorine. Male goats raised in the area adjacent to the factory showed significant increase in the level of these two elements in the serum. Estimation of cadmium level in serum male goats showed significant increase in the exposed area (0.25 ± 0.06 mg/l)

when compared with the level in the control area (0.018 ± 0.003 mg/l). This result was higher than that recorded previously at the same area (0.0075 mg/l and 0.0085 mg/l) by Seddek, (1988) and Sayed, (2001) respectively.

The serum fluorine level in goats at the exposed area showed significant increase (0.12 ± 0.01 mg/l) when compared with the level in the control area (0.05 ± 0.005 mg/l). This result

was nearly similar to that recorded previously at the same area ($0.17 \pm 0.01 \text{ mg/l}$) by Sayed, (2001).

Cadmium and fluorine can affect male reproductive functions including alteration in the circulating levels of several hormones (e.g., testosterone, LH, FSH) (Lafuente *et al.*, 2004), decreased level of testosterone and inhibition of spermatogenesis (Bedwal and Baghuana, 1994), reducing sperm counts, motility and morphology (Narayana and Chinoy, 1994; Arabi and Heydarnejad, 2007 and Siu *et al.*, 2009).

The results of this study clearly demonstrated that the mean levels of testosterone in male goats collected from areas around the factory were significantly decreased when compared with male goats in control area. Bedwal and Baghuana, (1994) reported that fluorosis in rats lead to zinc deficiency which firstly impairs angiotensin converting enzyme (ACE) activity and this in turn lead to a depletion of testosterone and inhibition of spermatogenesis. Siu *et al.*, (2009) reported that prolonged exposure to cadmium declining fertility in man and animals by reducing sperm count, testis function and testosterone synthesis. Previous studies have shown that Cd impairs the testosterone production in isolated Leydig cells without affecting their viability (Laskey and Phelps, 1991). Also Cd can modify hormone levels by affecting the hypothalamic-pituitary-testicular axis in different aspects, not only via its effects on Leydig cells. For instance, Cd affected the circadian pattern release of

noradrenaline, a regulator of hypothalamus hormone secretion, which resulted in changes in the daily pattern of plasma testosterone and LH levels (Lafuente *et al.*, 2004).

In the present study, the mean level of serum PAP in male goats collected from areas around the factory was significantly increased when compared with male goats in control area. The results were coincident with the study conducted by Obianime and Roberts, (2009) that cadmium toxicity caused a dose-dependent increase in the serum concentration of the PAP in the Wistar rats. Also similar results obtained by Asagba *et al.*, (2007) reported that chronic exposure of male Wistar albino rats to cadmium caused a significant increase PAP activity in the prostate, but a decreased body weight gain of the rats and organ/body weight ratio for prostate and testis compared to the Cd-free control. Our results similar to the results obtained by Monsefi *et al.*, (2010) who studied the effects of cadmium on male reproductive system in adult male mice. They found that PAP activity increased significantly in serum of animals receiving 50 mg/kg cadmium chloride. Our histopathological results demonstrated edema, fibrosis and hyperplasia of the prostate gland. The PAP activity in serum is an important diagnostic indicator of prostate cancer. An elevated level of PAP in serum has been used as a marker of prostatic cancer for many years. Serum PAP has been used as a tumor marker for diagnosis, staging and monitoring of prostate cancer (Ostrowsk, 1980; Heller, 1987 and Chu and Lin, 1998).

The testis is extremely sensitive to Cd toxicity (Siu *et al.*, 2009). In the present study, histopathological findings in the testicle of male goat of the exposed group revealed testicular degeneration with formation of spermatid giant cells. Congestion of the blood vessel, edema and fibrosis of the interstitial tissue with formation of spermatid granuloma were noticed. Similarly, Li and Heindel, (1998) reported that in vivo acute exposure to Cd caused blood testes barrier (BTB) disruption, germ cell loss, testicular edema, hemorrhage, necrosis, and sterility in several mammalian species (e.g., rodents, rabbit, dog, calf, stallion) and in vitro studies have illustrated Cd induced damage to testicular cells. Also, Obianime and Roberts, (2009) and Fouad *et al.*, (2009) studied the histopathological effect of Cd on the testes of the rat. These were characterized by vascular congestion, vacuolation, destruction of the germinal epithelial layers, focal necrosis and edema of the seminiferous tubules and reduction of spermatogenesis. In parallel, Monsefi *et al.*, (2010) showed a severe necrosis and atrophy in the testis of male mice that received 50 mg/kg of cadmium chloride in 0.5 ml distilled water for 45 days.

The epididymis showed edema, fibrosis and necrosis of the epididymal tubules. Similarly results obtained by Susheela and Kumar, (1991) who studied the effect of chronic fluoride toxicity in rabbits. They found that 18 or 29 months of toxicity induced loss of cilia on the epithelial cells lining the lumen of the ductuli efferentes of the caput epididymidis. Arabi and

Heydarnejad, (2007) reported that Cd induced membrane impairments, lowered motility, DNA breaks and a decreased rate in the acrosome reaction of bull spermatozoa, leading to sperm dysfunction. Presence of Cd in the male gonads and seminal plasma may exert deleterious effects on the animal sperm cells. Also, Narayana and Chinoy, (1994) reported reduced sperm acrosomal hyaluronidase and acrosin, an increase in acrosomal damage, a decline in sperm motility and decrease in cauda epididymal sperm counts in rats receiving sodium fluoride 10 mg/Kg body weight for 50 days by gavages.

CONCLUSION:

Testes were greatly targeted to the damage induced by Cd and flourine intoxication. Along with evidence derived from our study, where exposure to Cd and flourine constitutes a great threat being associated with reproductive injurious effects. Hence, concern should be directed to transfer the superphosphate factory in an area away from animals and humans to limit the Cd and flourine intoxication.

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دراسات سمية باثولوجية على التأثيرات الناتجة عن المعادن الثقيلة المنبعثة من مصنع السوبرفوسفات على الكفاءة التناسلية في ذكور الماعز

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** قسم الباثولوجيا والباثولوجيا الإكلينيكية- كلية الطب البيطري- جامعة أسبوط

صممت هذه الدراسة لتقييم التأثيرات السمية الباثولوجية للمعادن الثقيلة المنبعثة من مصنع السوبرفوسفات بمدينة منقباد - أسبوط على الكفاءة التناسلية لذكور الماعز. وقد تم اختيار ثلاثين ذكر ماعز من منطقة جزيرة الأكراد الملاصقة للمصنع وخمس ذكور ماعز اختيرت من مدينة ديربوط البعيدة عن المصنع بحوالى ٦٠ كيلو متر شمالا. تم أخذ عينات مصل من ذكور الماعز لقياس مستوى الكاديوم والفلورين وكذلك هرمون التستستيرون وإنزيم الفوسفاتيز الحامضى البروستاتى. كما تم أخذ عينات من أنسجة الخصية والبربخ وغدة البروستاتا للفحص الباثولوجى. وقد أظهرت النتائج ارتفاع معنوى فى مستوى الكاديوم والفلورين فى أمصال الحيوانات الملاصقة للمصنع والمعرضة للتلوث مقارنة بالحيوانات البعيدة عن المصنع. كما لوحظ نقص فى مستوى هرمون التستستيرون وزيادة فى أنزيم البروستاتيك أسيد فوسفاتيز فى الحيوانات المعرضة للتلوث عنها فى الحيوانات البعيدة عن المصنع. وقد أظهر الفحص الباثولوجى وجود استحالات فى أنابيب الخصية مصحوبة باحتقان وأديما وكذلك تليف فى الأنسجة البينية. كما لوحظ وجود تورمات مزمنة نتيجة خروج الحيوانات المنوية من خارج أنابيب الخصية. كما لوحظ وجود أديما وتليف وكذلك تنكز فى البربخ وأديما وتليف وتكثر نسيجى فى غدة البروستاتا . وقد أوضحت الدراسة أن التعرض للتلوث بالكاديوم والفلورين المنبعثة من المصنع تؤدي إلى أثار ضارة على الكفاءة التناسلية مع وجود اضطرابات هرمونية وبياثولوجية.