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# Histopathological effects of $CdSO_4$ on foetal liver kidneys and heart of albino rats.

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**ABSTRACT**

This study deals with the toxic impacts of cadmium on some foetal organs of Virgin albino rats. The histopathological study revealed that cadmium causes congestion of the blood vessels and blood sinusoids, hemorrhagic foci degeneration , cytoplasmic vaculation and pyknosis in hepatic cells of the liver, congestion of blood vessels, and cardiac hypertrophy represented as loose and separated cardiac muscle fibers of the heart. There is also destruction of some cells of the proximal and distal tubules of the kidney, and the collecting tubules exhibit extensive degeneration with cytoplasmic vaculation.

**Keywords:** Cadmium, liver, kidneys and heart

## INTRODUCTION

It is well documented that different environmental pollutants including industrial wastes, insecticides, pesticides … etc have deleterious impacts on different biological activities. Pollution with toxic metals has increased since the beginning of the industrial revolution. Pollution with cadmium is of particular concern because it accumulates in the human body with a half-life exceeding 10 years (Kelley1999) and has been linked with a number of health problems, including renal tubular dysfunction (Staessen *et al*. 1999), osteoporosis (Fujita 1992), ovarian dysfunction ,(Paksy *et al*.1992) , testicular tumorgenesis ( Waalkes *et al*.1996) and cardiovascular disorders(Mustafa *et al*.2000). In a previous study (Hefny & Ahmed 2001) the impact of Cd toxicity on the fetus of pregnant rats caused significant reduction in body weight and morphological abnormalities such as exencephaly, gastroschisis, kinky tail and club foot. Cadmium also reduced the length of the long bones and caused retardation of ossification. In hamster embryos malformations included exencephaly, microphthalmia, cleft lip, cleft palate, gastroschisis and umbilical hernia which dependent upon the stage of organogenesis during which cadmium exposure occurs (Samarawickarama & Webb 1981). Ahokas & Dilts (1980) observed that cadmium easily crosses the placental barrier in laboratory animals in early gestation. In an extension to the pervious studies, the current study was undertaken to investigate the histopathological effects of Cd on some body organs of rat embryos.

## MATERIALS AND METHODS

Female albino rats weighing 150-200 g were obtained from the National Research Centre, Cairo, Egypt. The females were introduced into the male cages. The morning when sperm were detected in a vaginal smear (indicating successful mating) was considered to be day zero of gestation. The pregnant animals were divided into two groups, 10 animals in each group. The first group served as a control and were injected with 0.9 % NaCl on the $8^{th}$ day of gestation The second group were injected intraperitoneally with a single dose (2mg /kg) of $CdSO_4$ on the $8^{th}$ day of gestation .The selection of this dose depended on pilot tests. All the animal were killed on the $20^{th}$ day of gestation and fixed in 10% formalin for

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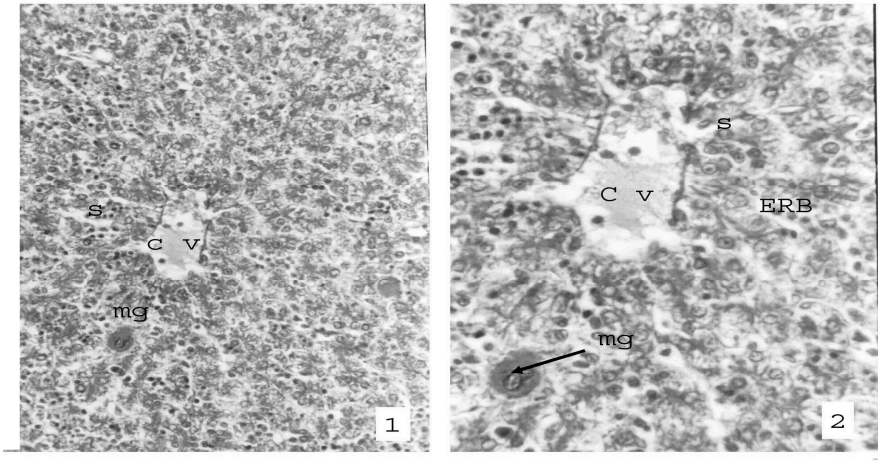
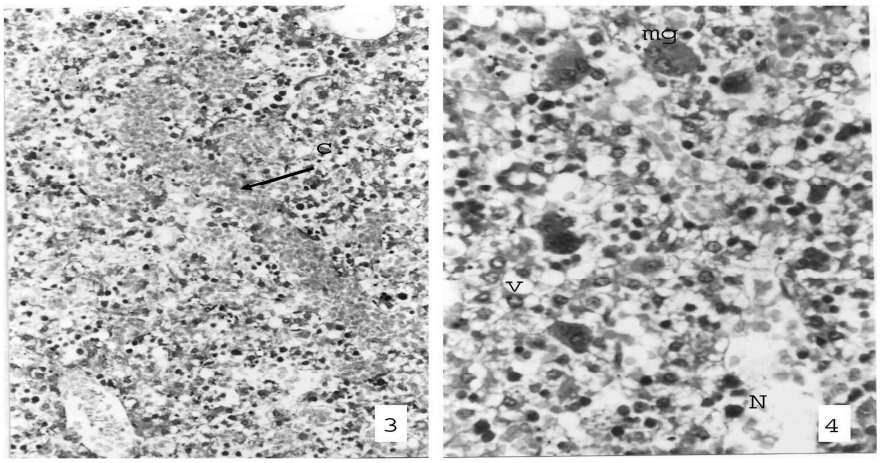
histopathological study. The liver, heart, and kidney were removed from both control and treated fetuses and fixed in 10% formalin for histopathological study. They were dehydrated in ascending series of ethyl alcohol, cleared in xylol and embedded in paraffin wax at 58-60ºC. Sections of 6 micrometers thick were prepared, mounted on clean glass slides and kept in an incubator at 37ºC to dry for 24 hours. Sections were stained with haematoxylin and eosin, dehydrated with ascending series of alcohol, cleared with xylol and mounted in Canada balsam.

## RESULTS

The liver of embryos of the control group displayed the histological features of the normal liver (Figures 1 & 2) .the cadmium-treated liver showed marked congestion of the blood vessels and blood sinusoids, through which blood had escaped, producing hemorrhagic foci. Degeneration, cytoplasmic vaculation and pyknosis were evident in hepatic cells (Figures 3 & 4).

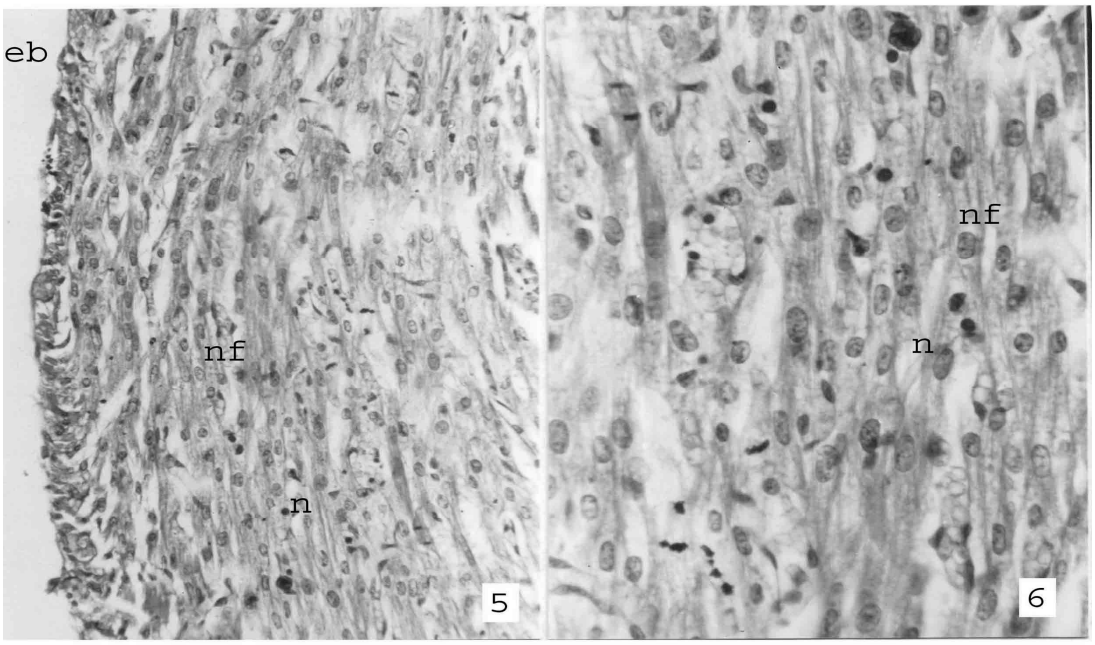



Figs 1& 2: Photomicrograph (Fig 1) and enlargement (Fig 2) of section of control fetal liver showing normal hepatocytes (HC) alternating with blood sinusoids (S) that converge toward the central vein (CV); the hepatic cords and blood sinusoids contain blood. There are a few giant cells megakaryocytes (MG). (200x & 400x)

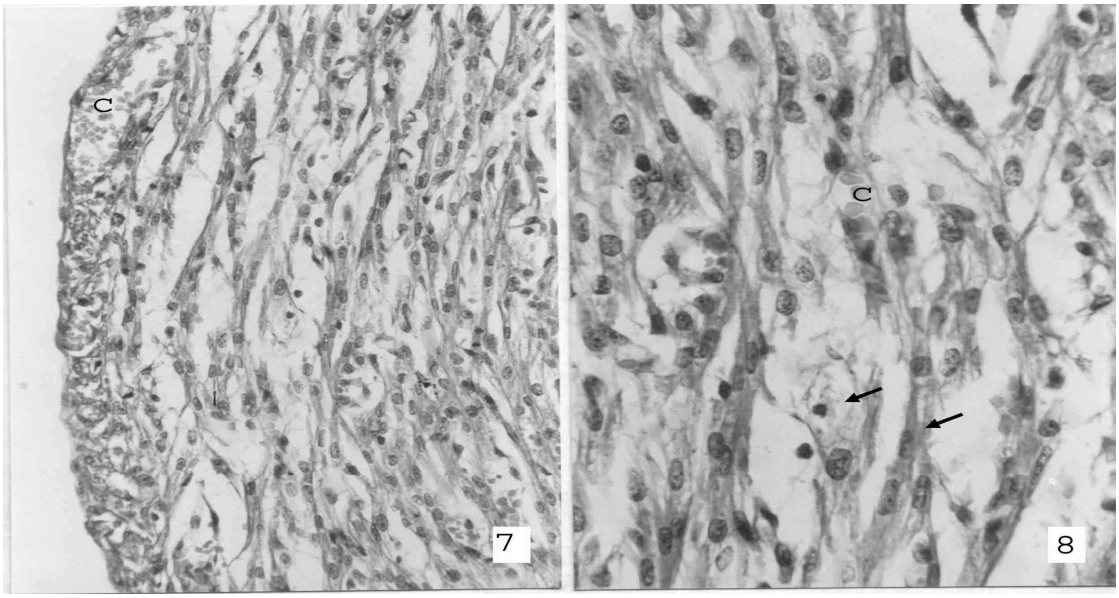



Figs 3& 4: Photomicrographs of sections of maternally Cd-treated fetal liver showing congestion of blood sinusoids (C) , numerous large vacuoles (V) scattered in the cytoplasm of the hepatocytes, some necrotic cells (N) with darkly stained nucleus and an increase in the number of megakaryocytes. (200 x & 400x)

The heart of control embryos displayed the histological features of the normal heart (Figures 5 & 6) . Cadmium-treated hearts showed distinctive congestion of blood vessels and cardiac hypertrophy, seen as loose and separated cardiac muscle fibers (Figures 7 & 8).

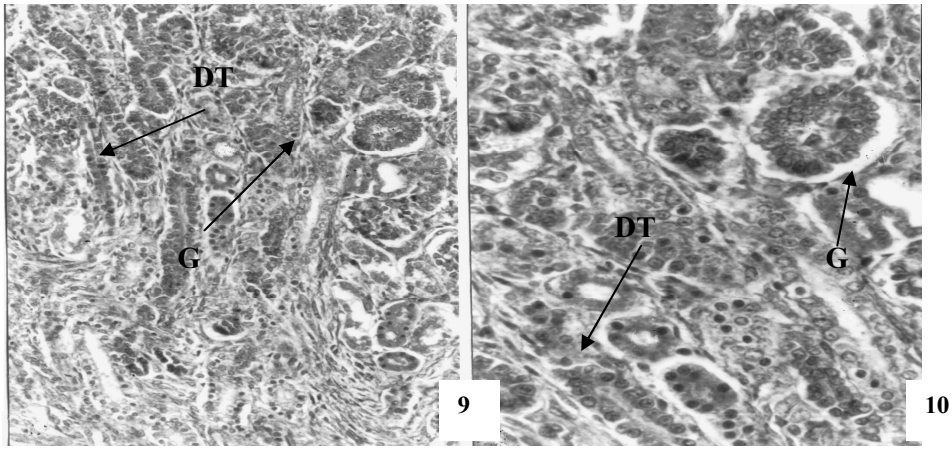



Figs 5 & 6: Photomicrographs of sections of control fetal cardiac muscles showing epicardium (ep) and myocardium muscle fibre (mf) which possesses a number of ovoid and central nuclei (n).(200x & 400x).

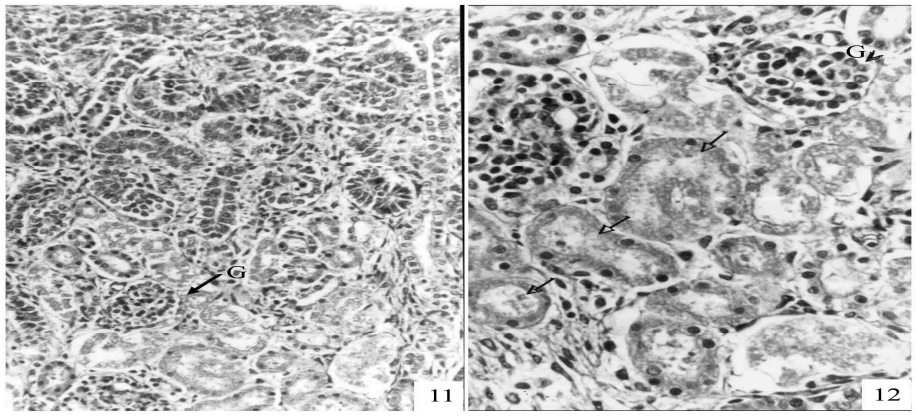



Figs 7& 8: Photomicrographs of sections of maternally Cd-treated fetal heart showing congestion of blood vessels (C) and cardiac hypertrophy which is represented as loose and separated cardiac muscle fibres (arrow).(200x & 400x).

The kidney of control embryos displayed the histological features of the normal kidney (Figures 9, 10 &13). The kidney of Cd-treated embryos showed destruction of some cells of the proximal and distal tubules, and the collecting tubules exhibited extensive degeneration and cytoplasmic vaculation (Figures 11, 12 & 14).




Figs 9 & 10: Photomicrographs of section of the control fetal kidney, showing Bowman's capsule (B.C). glomerulus (G), proximal (PT) and distal (DT) convoluted tubules and collecting tubules (CT).(200x & 400x).




Figs 11& 12: Photomicrographs of sections of the Cd-treated maternally fetal kidney. Showing degeneration of some cells of the proximal and distal tubules (arrow), as well as swelling of the glomerulus (arrow head) (200x & 400x).

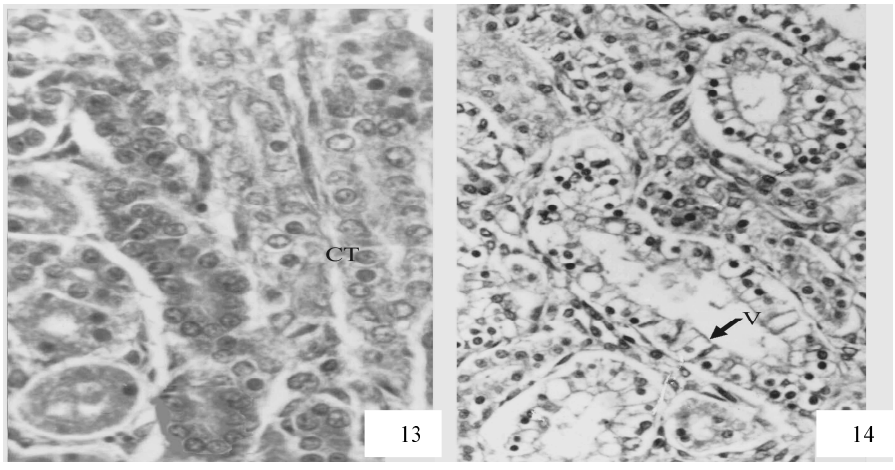



Fig 13: Photomicrographs of section of the control fetal medullary region showing normal structure of the medulla and normal collecting tubules (CT). (400x)
Fig 14: Photomicrographs of section of Cd-treated fetal medullary region showing necrotic cells (N) of some collecting tubules represented by vaculation (V) of the cytoplasm and pyknotic nuclei (400x).

## DISCUSSION

Cadmium whether inhaled, ingested or injected is toxic to virtually every system in the body. It is a major environmental and occupational hazard because of its widespread use in industry and subsequent release into the environment (Dobson. 1992; Friberg et *al.* 1992). Cadmium may be an etiological factor for various pathological processes including testicular tumour, renal dysfunction, growth inhibition, cancer and hypertension (Balaraman *et al.* 1996). The most striking toxic effects of Cd intoxication are renal tubular dysfunction (Robinson *et al.* 1993) and cardiovascular abnormalities (Moustafa et *al.* 2000).

Cadmium in the blood bound to red blood cells and high molecular weight proteins in plasma, particularly albumin. A small fraction of cadmium may be bound by metallothonine blood (Amdur et *al*. 1994).

From the site of cadmium absorption the blood transport cadmium to the liver, where it induces the synthesis of metallothionine, a zinc storage protein, that affects toxicity (Suzuki 1982). The cadmium-metallothionine complex is released from the liver and transported via the blood to the kidneys where it may dissociate within the tubular cells. The resulting free metal induces intracellular synthesis of metallothionine which binds free intracellular cadmium for protection against toxicity, at least until the binding protein is saturated (Ellis *et al.* 1985).

New born infants have low body content of cadmium, usually less than 1mg total body burden. The placenta synthesizes metallothionine and probably serves as barrier to maternal cadmium, but the fetus can be exposed to maternal cadmium with increased maternal exposure (Amdur *et al.* 1994). The placenta concentrates cadmium greatly (Miller 1983) causing damage and placental necrosis (Holmberg&Ferm 1969). Furthermore, cadmium when injected into hamsters on the eighth day of gestation is highly teratogenic, resulting in facial malformations (cleft palate, anophthalmia, microphthalmia, exencephaly) and resorptions (Mulvihi *et al.* 1970). Significant amounts of cadmium were detected in the day 8 embryo within 24 h following maternal administration ( Ferm et *al.* 1969 , Clarkson *et al*. 1983). Single injections of cadmium late in the gestation of mice and rats will produce fetal lethality, growth retardation and placental necrosis within 18-24h ( Ahokas *et al.* 1980, Samarawickarama & Webb 1979, Levin & Miller, 1980). Pre - and postnatal exposure to cadmium have been suggested to alter ovarian function and reduce estrogen production, leading to changes in the progression of normal gestation in females (Parizek *et al.* 1968, Der *et al.* 1977).

The liver of maternally treated fetuses showed a marked congestion of the blood vessels and blood sinusoids through which blood escaped producing hemorrhagic foci, degeneration of hepatic cells. The hepatic cells exhibited vacuolated cytoplasm and pyknotic cells which possessed shrunken nuclei. Sarkar *et al.* (1994) found that cadmium may induce oxidative damage in hepatic cells. Sauer *et al.* (1997) reported that 24h after administration, $CdCI_2$ produced multifocal hepatocellular necrosis and increased plasma GPT activity. Bokori *et al.* (1995) studied the effect of cadmium on Broiler-Chickens and they also reported that cadmium caused liver and kidney degeneration, myocardial hypertrophy and cardiac dilatation.

The susceptibility to lipid peroxidation of liver, kidney, brain, testis, lung and heart was investigated in tissue homogenates incubated with various concentrations of Cd by Manca *et al*. (1991a,b). They found that the liver, heart, and testis showed the greatest

release of breakdown products of cell components from Cd exposure compared to control levels, and lipid peroxidation significantly increased in the majority of tissues.

In the heart of maternally treated fetuses there is a distinctive congestion of blood vessels and hypertrophy of the cardiac muscle. E1-Hady and E1-Sabbagh (1995) also reported that cadmium caused anomalies in the heart, and Kleinfeld *et al.* (1955) observed that the administration of cadmium on isolated frog heart caused atrial dilatation. Moustafa *et al.* (2000) reported that hepatic cellular damage was induced by cadmium chloride as shown by their effect in increasing the levels of both hepatic Ca and serum aminotransferases (SGPT &GOT) and reducing hepatic total protein 24-hrs post-treatment . (Li *et al.* 1997) recommended that the oxidative destruction of polyunsaturated fatty acids of membrane phospholipids, a phenomenon generally termed lipid peroxidation is considered to be an important mechanism of toxicity for cadmium.

In the kidney of the maternally treated fetuses the current results show that cadmium causes destruction of some cells of the proximal and distal tubules, and the collecting tubules exhibit extensive degeneration through cytoplasmic vaculation. Li *et al.* (1997) also found that the kidneys of cadmium-administered rats were affected showing atrophy, dilatation, fibrosis of tubules and a large quantity of degenerated necrotic and recuperative tissues. It is worth mentioning that although binding of cadmium by metallothionine in the liver may protect other organs, the cadmium-metallothionine complex is readily taken up by kidneys producing pathological lesions (Wedeen & Batuman l983, Dudley *et al*. 1985). Johns *et al.* (1923) had found that the kidney retains more cadmium than other organs, and the kidney has been reported to be one of the organs that seriously damaged due to exposures to cadmium oxide in fatal stage (Kazantzis *et al.* 1963). Long-term exposure to low levels of cadmium also causes serious effects. For instance, it has been reported to cause chronic renal tubular disease, and there may also be effects on the cardiovascular system and skeletal muscles (Friberg *et al*.1986).

The toxicity of heavy metals may be due to the hemolytic fission of hydroperoxides, and free-radical and lipid peroxidation (Dougherty & Hoekstra 1997). The peroxidation damage to the cellular membranes may be caused by Cd-induced free-radical generation that eventually leads to injury to the cell membrane and damage of subcellular organelles (Sarkar *et al.*1995).

It can be concluded from this study that the adverse actions of cadmium involve a multiplicity of target organs and systems. Cd intoxication alters many aspects of cell functions. This suggests mainly as a result of its effect on free-radical formation and induction of oxidative stress. This eventually leads to changes in the permeability of the cell membrane and to the dysfunction of the cellular components and disturbance in metabolic pathways**.**

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## الملخص العربى

### التأثيرات النسيجية المرضية لكبريتات الكدميوم على أجنة الفئران البيضاء

**هانئ أحمد حفني – شريفة حامد أحمد**
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تهدف الدر اسه إلى معرفه تأثير كبريتات الكادميوم على التركيب النسيجي لكل من الكبد والقلب والكليتين لأجنة الجرز الأبيض وقد تم اختيار الفئران للتزاوج من المركز القومي للبحوث والتي تزن من(١٥٠جم) إلى (٢٠٠جم) , وقد وزعت الجرذان على مجموعتين المجموعة الأولى تمثل الحيوانات الضابطة وقد تم حقنها بمحلول ٩. % كلوريد الصوديوم في اليوم الثامن من الحمل ، ولمجموعه الثانية حقنت بمحلول كبريتات الصوديوم ( ٢ ملجم / كجم ) في اليوم الثامن من الحمل أيضا" أظهرا تلك الدراسة أن التعرض لكبريتات الكادميوم يكون مرتبط بتغيرات نسيجيه مرضيه واضحة في كل من الكبد والقلب والكليتين لأجنه الجرذ الأبيض متمثلة في احتقان الأوعية الدموية وتحلل أنسجة الكبد، وظهور فجوات في الخلايا الكبدية.

أما بالنسبة لتأثير الكدميوم على القلب فكان متمثلاً في تضخم عضلة القلب واحتقان الأوعية الدموية، وفي الكلية وجد تحلل في الأنسجة وكذلك احتقان في الأوعية الدموية مع وجود فجوات في نسيج الكلية . ومن خلال هذه الدراسة يمكن استنتاج أن للكادميوم تأثيرات سامة عديدة تشمل الكبد والقلب والكلية .