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# CONTENTS

# THE TOXIC EFFECT OF CADMIUM ON A LIVING ORGANISM AND ITS DETOXIFICATION BY ZINC IONS.

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***Annotation.*** *A review of data on the effects of cadmium on living organisms is presented. Cadmium (Cd) is an environmental toxicant and a metabolic disturbance in organs and tissues in humans. Cadmium compounds pathologically affect the liver, kidneys, cardiovascular system and embryogenesis. The negative effects of cadmium salts on the reproductive system are manifested in the violation of the function of germ cells, affect the fertilization and development of the early embryo, which is extremely sensitive to toxicity of heavy metals. Modern researchers are actively searching for bioantogonists of toxicity to heavy metal salts. Zinc is an essential element and its compounds in the body have antagonistic characteristics of the toxicological properties of cadmium compounds. Therefore, the study of the toxicological characteristics of cadmium compounds and the search for its bioantogonists is an urgent problem of modern biology and medicine.*

***Key words:*** *cadmium, zinc, toxicity, liver, experiment.*

Cadmium and its compounds are one of the most toxic heavy metals in the environment. It ranks seventh in the list of hazardous substances compiled by the US Agency for Toxic Substances and Disease Registration [43]. The widespread use of cadmium compounds in industry has led to a high level of accumulation of this ecovolume in biological systems on the planet. The population may be exposed to cadmium through the use of food and drinking water containing its particles, inhalation of air, when exposed to tobacco smoke. Cadmium has a long half-life from the human body (~ 20–40 years) [46]. This metal accumulates in human and animal tissues, the main organs of accumulation are the liver, kidneys and ovaries [35]. Cadmium has a negative effect on the liver, kidneys, cardiovascular system [21] and the reproductive organs in adults, including the ovaries and testicles, which are sensitive to cadmium toxicity because the latter passes through the hematotesticular barrier [40].

The purpose of this review of scientific literature was to analyze the experimental and clinical results of the study of the effect of various doses of cadmium compounds on organs and organ systems with different methods of penetration of the toxicant.

**The effect of cadmium on male reproductive organs.** The introduction of cadmium to experimental animals showed the presence of inflammatory processes in the testes [13]. It is capable of exerting toxic effects on two types of cells located in

the testes, on Sertoli cells and on Leydig cells [8]. Cadmium ions have the ability to displace various ions from their position in biological molecules. Thus, the activity of the molecules where metal was replaced by cadmium changes, and biological processes can be inhibited [3], up to the violation of the hematotesticular barrier [45].

It has been proven that cadmium plays an important role in the initiation of oxidative stress in a living organism. It causes the formation of reactive oxygen species not directly. One of the mechanisms of its action is the inhibition of the antioxidant system of the body, due to the displacement of cuprum and zinc from the active centers of antioxidant enzymes. This leads to inactivation of enzymes, an increase in the number of reactive oxygen species such as superoxide anion, hydrogen peroxide, and hydroxyl radicals. Active forms of oxygen oxidize proteins, DNA, which ultimately leads to cell death [23, 44].

**The effect of cadmium on the female reproductive system.** With age, the concentration of cadmium in the ovaries increases, it affects the development of oocytes and causes a violation of ovulation [41]. According to published data, the oral exposure of cadmium to rats caused damage to the ovaries and violation of plasma sex hormone levels, which most likely led to morphometric changes in the endometrium and / or disturbances in the phases of the genital cycle [26]. Modern researchers have identified violations of the concentration of estradiol in plasma and uterus, as well as violations of the estrous cycle. These effects, as well as increased lipid peroxidation in the uterus and ovary, were observed within six months after cessation of cadmium exposure [25]. The introduction of cadmium leads to histopathological changes in the ovary (follicular maturation, follicular atresia, corpus luteum degeneration, damaged and less numerous oocytes and degeneration of granulosa cells) and the uterus (increased lumen epithelium and endometrial thickness, interstitial edema, capillary changes) [26]. Also, this metal is capable of causing disturbances in the process of embryo implantation [1].

**The effect of cadmium on embryogenesis.** During pregnancy, the body has a high degree of susceptibility to teratogenic factors, one of which is cadmium. In in vivo experiments on Parizek rats, it was shown that the administration of cadmium once at a dose of 40 μM / kg leads to the destruction of the embryonic part of the placenta and to the death of most embryos. There is evidence of an experiment on rats of the Wistar-Porton line. Their gestation period is 21 days. They were given cadmium at a dose of LD50. on the twentieth day of pregnancy. Death was observed within 16-24 hours after cadmium administration. Immediately after cadmium administration, redness of the extremities, rapid breathing, apathy and lethargy of muscles were noted. The predominant pathological lesion was subpleural hemorrhage of the lung. Palpation, immediately after the animal has stopped breathing, reveals that the heart is still beating, and this discovery suggests respiratory paralysis. Pregnant animals who died 16 to 24 hours after cadmium administration had vaginal bleeding, which indicates damage to the placenta. The liver and kidneys are edematous and hyperemic, the fruits are pale in color [35]. Histological studies showed that the placenta lost its architecture and turned into an extensive blood clot.

Cadmium compounds have a strong teratogenic effect. So hydrocephalus,

anophthalmia, microphthalmia, gastroschisis and umbilical hernia were revealed. According to published scientific experimental literature data, serious malformations have been identified in golden hamster embryos. These malformations consisted of a specific effect on the face and upper jaw, ranging from a simple mid-line cleft t.o almost complete obliteration of normal facial architecture.. Were also found anophthalmia, digital and other limb defects, rib fusions and exencephaly [12].

It has been proven that cadmium accumulating in the placenta can interfere with the transport of nutrients and oxygen to the fetus [20,24,36]

Recent experimental data have shown that cadmium accumulates in embryos starting from the four-cell stage and above. Exposure to high doses of metal can slow the progression of the embryo to the blastocyst stage. It can also lead to degeneration and decomposition in blastocysts and cause apoptosis and impaired cell adhesion. After implantation with the introduction of cadmium, a wide range of disorders in the embryo can be observed, depending on the stage of exposure and dose. Thus, craniofacial, neurological, cardiovascular, gastrointestinal, urogenital and urogenital anomalies and limb anomalies were described [41]. In addition, a decrease in fetal mass and a decrease in the length of the hind and forelimbs were noted compared with the control [1].

**The effect of cadmium on the liver.** The liver plays a huge role during pregnancy in the formation of fetal health. The introduction of cadmium leads to a decrease in liver weight. Depending on the concentration of cadmium administered, changes in hemodynamics were noted in the liver, expressed as changes in the liver parenchyma, as well as changes in the functional activity of cells [34].

**The effect of cadmium on the kidneys.** Modern studies of the effects of cadmium and its compounds on organs have shown that cadmium has high nephrotoxicity, which in turn can lead to complications such as proteinuria, calciuria, aminoaciduria, glycosuria and tubular necrosis, terminal renal failure, early onset of diabetic complications of the kidneys, osteoporosis, dysregulation of blood pressure [38].

**The mechanisms of penetration of cadmium compounds in organs and tissues.** Cadmium ions are capable of ionic and molecular mimicry. Molecular mimicry refers to the ability of a metal ion to bond to an endogenous organic molecule to form an organic metal species that acts as a functional or structural mimic of essential molecules at the sites of transporters of those molecules. Ionic mimicry refers to the ability of a cationic form of a toxic metal to mimic an essential element or cationic species of an element at the site of a transporter of that element [3]. As a result of these mechanisms, subsequent effects of cadmium may include modulation of the concentration of ions in the cell and structural modification of target molecules with subsequent inhibition of their biological actions. Mimicry phenomena have been described in detail between Cd and Zn; there is evidence of mimicry between Cd and Mg, Ca, Cu, etc. [3,46]. For example, the negative effect of cadmium on the structure of bone tissue, in which this metal replaces calcium, is one of the reasons for the development of osteoporosis [15].

In its chemical properties, cadmium is similar to zinc, but in contrast to zinc, cadmium is Pearson's soft acid. In particular, in coordination compounds with thiocyanate ions,

cadmium (like mercury) binds to the ligand via the sulfur atom (Cd (SCN) 4) 2−, while in such complexes zinc is bound to the nitrogen atom, forming compounds such as (Zn (NCS ) 4) 2− [19]. Due to this similarity, cadmium can replace zinc in the active centers of enzymes leading to their dysfunction [42]. At the same time, cadmium compounds have more pronounced basic properties compared to similar zinc compounds, which are amphoteric. In addition, it was demonstrated that cadmium toxicity decreases in the presence of zinc [2], which also indicates competition between these ions for the active center of enzymes.

**Reducing the toxic effects of cadmium with zinc ions.** The toxic effects of cadmium, especially caused by low chronic doses of exposure, may be associated with altered homeostasis of some bioelements [16,28]. From the literature data it follows that in experimental animals, such as rats, mice, rabbits, there is an imbalance of zinc, cuprum and magnesium, under the influence of acute and subacute doses of cadmium [7].

Zinc is an indispensable trace element, it is involved in many aspects of cellular metabolism. It is necessary for the catalytic activity of many enzymes [37] and plays a role in protein synthesis, DNA synthesis, and cell division [30]. Zinc also supports normal growth and development during pregnancy, childhood and adolescence [10, 22, 39]. Despite the fact that cadmium ions are capable of replacing zinc ions in biological molecules and are similar to zinc in chemical properties, the combined use of these two metals leads to a decrease in the teratogenic effect caused by cadmium [11].

That Zn supplementation during exposure to Cd may have a protective effect on lipid metabolism consisting in its ability to prevent hyperlipidemia, including especially hypercholesterolemia, and to protect from lipid peroxidation. The findings seem to suggest that enhanced dietary Zn intake during Cd exposure, via preventing alterations in the body status of lipids may, at least partly, protect against some effects of Cd toxicity, including oxidative damage to the cellular membranes and atherogenic action [31,32,33].

Cadmium is a well-studied inducer of cell necrosis and apoptosis. Zinc is known to inhibit apoptosis caused by toxicants, including cadmium, both in vitro and in vivo [27]. Zinc has antioxidant, anti-apoptotic and anti-inflammatory properties, and is also able to stimulate regenerative processes and reduce cadmium levels in the liver [31, 17]. The combined management of zinc and cadmium prevents the accumulation of cadmium in the kidneys in rabbits [29]. In addition, zinc supplements reduce the risk of bone fractures, as well as increase bone density in animals poisoned with cadmium for six months [4,5,6]. The protective role of zinc against cadmium toxicity has been well studied and can be explained by the ability of zinc to reduce the degree of oxidative stress, apoptosis and necrosis caused by cadmium [14,18,32,33]. It was also found that zinc is able to enhance the immune function and proliferation of rat lymphocytes treated with cadmium [9].

**Conclusions.** The results of studies involving laboratory animals, cell cultures, as well as human clinical data confirm the toxic role of cadmium in relation to organs and tissues, as well as embryonic development. Understanding the nature and mechanisms of action of cadmium compounds makes it possible to develop methods for the correction of environmentally-related disorders occurring in a living organism. Including the use

of zinc ions, which are able to reduce the teratogenic effect of cadmium compounds and can act as a biantogonist for cadmium.

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