

A short overview about cadmium and its toxicity focused on humans, bioindicators and model organisms

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Abstract

According to Paracelsus (1493-1541) everything from this planet is poison, only the dose makes the poison to be harmless. Even the essential elements for life support are toxic for all organisms in high amounts. Mercury, cadmium, metalloids arsenic and lead were responsible for poisoning and death of many humans and life forms from this planet for centuries. Cadmium forms different compounds that are used in industry for electroplating, pigments, plastic stabilizers, Ni-Cd rechargeable batteries, semiconductors, solar cells. According to literature, human's intake the highest amount of cadmium from cigarettes smoking and food. The level of cadmium in bird's bodies is important to analyze the environmental health. Birds are very sensitive to environmental changes and pollutants. This short overview investigated the pollution sources and pathways of cadmium within environment, its toxicity, symptoms and diseases focused on humans and other organisms. Some possible cure for humans' acute and chronic exposure to cadmium was searched in different studies.

Keywords: Cadmium, Human exposure, Sources, Pathways, Toxicity

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Introduction

Cadmium is a metal element with the atomic number 48 and symbol Cd. It has 64 neutrons, 48 protons/electrons, the melting point is 320.9°C (594.05K, 609.62°F) and the boiling point is 765°C (1038.05K, 1409.62°F). Its crystal structure is hexagonal, color silvery and oxidation states 21(Nordberg *et al.*, 2009). According to Paracelsus (1493-1541) everything from this planet is poison, only the dose makes the poison to be harmless. Even the elements essential for life support are toxic for all organisms when in high doses. Mercury, cadmium, metalloid arsenic and lead were responsible for poisoning and death of many humans and life forms from this planet for centuries. Studies revealed that the need for the metals at global scale started with the Industrial Revolution and the technological development (Goldberg *et al.*, 1977; Kähkönen *et al.*, 1998). These phenomena released important quantities of high toxic compounds in air, water and land, with no possibility to defense against them. Cadmium is one of these poisons with devastating effects for human health and other life forms.

This short overview investigated the pollution sources and pathways of cadmium within environment, its toxicity, symptoms and diseases in humans and other organisms. A literature research was performed in order to find some possible cure for acute and chronic exposure to cadmium in humans.

Sources of cadmium in environment

Cadmium is extremely toxic for all life forms from this planet. It was discovered by F. Stromeyer, a German chemist in 1817 (Nordberg *et al.*, 2009). Cadmium forms different compounds that are used in industry for electroplating, pigments, plastic stabilizers, Ni-Cd rechargeable batteries, semiconductors, solar cells (Hooser *et al.*, 2012). It naturally occurs in environment together with lead, copper and zinc at low levels; all types of rocks and soils contain some cadmium. Anthropogenic activities are the main sources of cadmium pollution: coal combustion, zinc smelting and refining, mine wastes, the use of rock phosphate and sludge in agriculture, iron and steel production (Hooser *et al.*, 2012), waste disposal and cars traffic. It is absorbed from these sources by the organisms and, afterwards, can be concentrated along the food webs.

Human exposure, toxicity and disease

Cadmium has a biological half-life of 10-30 years (Nordberg *et al.*, 1996; Satarug *et al.*, 2006; Satarug *et al.*, 2012) higher than lead 5-20 years (Chen *et al.*, 2014). The chronic exposure with cadmium it is responsible for the Itai-itai disease. Inaba *et al.*, 2005 described this disease which is caused by the chronic poisoning with cadmium and the damages for the human body are: kidney and glomerular dysfunctions, bones damage associated with osteoporosis and osteomalacia. The first symptoms are femoral bone pain

followed by spine and ribs pain. Patients that suffer the advanced level of the disease cannot walk because of the intensive bones pain and they are forced to remain in bed. The fractures are common in this disease.

The first mass poisoning with this metal was known after World War II in Toyama, Japan, when the Jinzu River was contaminated with cadmium released from mining activities (Inaba *et al.*, 2005).

Humans intake the highest amount of cadmium (Fig. 1) from cigarettes smoking and food (Andujar *et al.*, 2010; Faramawi *et al.*, 2012; Menai *et al.*, 2012; Rahimi *et al.*, 2013; Santos *et al.*, 2013; Rahbar *et al.*, 2014; Rambousková *et al.*, 2014; Sebastian *et al.*, 2014). Cadmium is present in large amounts in cigarettes (1-2 μg in a standard cigarette). A smoker absorbs 10-30% of this by inhalation because tobacco intensively extracts cadmium from soil and accumulates it in the leaves (Andujar *et al.*, 2010).

Approximately 80% of cadmium absorbed in the human body is from food resources (Järup *et al.*, 2009). The element was found in high concentrations in: seafood, potatoes, leafy vegetables, grains and cereals. Uncontaminated food could be easily poisoned with cadmium from cookware. Weidenhamer *et al.*, 2014 explained in their study how toxic are the aluminum cookware and utensils

manufactured by the local artisans from Cameroon. Also Romanians have many traditional dishes cooked in handmade aluminum cookware. It is possible that in Romania to be the same situation like in the study made in Cameroon or worse. Cookware are made from recycled aluminum parts from old cars and from scrap yards which are melted together without a properly purification of other extremely toxic metals. In the aluminum parts could be found cadmium which very easily contaminates the food. In the above mentioned study, the authors presented the importance of the food pH that is cooked in these pots. Food with an acid pH close to 4 can dissolve and release cadmium from the pots very fast. They made an experiment with these pots to see how much cadmium is released in 24h (ambient temperature) and 2h (boiling) for a solution that simulated the food with an acid pH close to 4. The results were different for each pot because of the cadmium concentration in the cookware, the source of aluminum parts is very important. The cadmium range solution for 24h at ambient temperature was 0.4-97.6 $\mu\text{g L}^{-1}$ and for 2h boiling was 0.4-58.3 $\mu\text{g L}^{-1}$. Particles from the pots easily can contaminate the food. The level of contamination has many variables like: aluminum source and purification, cooking time, food's pH and mixing tools.

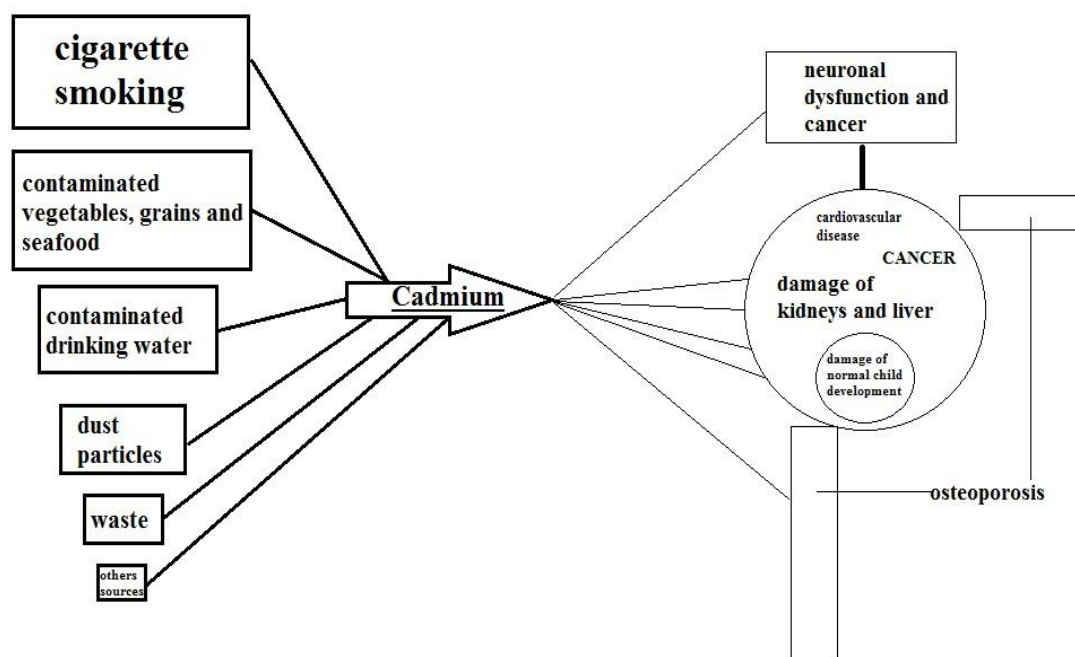


Figure 1: The sources with the highest risk of cadmium intake in the human body and the damages.

Many studies were focused on food contamination with cadmium and other toxic metals all around the world. Most of the samples were collected from species which are important in economical trade and their consumption has a direct influence upon consumer's health (Clemens *et al.*, 2013; Adams *et al.*, 2014). The contaminated food has no value and cannot be consumed. The healthy ecosystems will always provide quality food with the condition to have a balanced budget of nutrients.

The dust particles from the cities are a source of cadmium exposure for human health. In a city with industry and intensive cars traffic, cadmium particles are carried by air into the flats. The most exposed flats are those near the boulevards. The vegetation area between the streets and flats is very important because it may work as a biofilter for dust particles. The air

conditioner is good for filtering the air from outside to inside the flat, but it consumes energy and it might be not healthy for the lungs. The windows with mosquito nets may stop some dust. It is recommended periodic cleaning of the dust from the living rooms and cleaning the shoes before step in the house because they carry dust from outside to inside.

The effects on child development

The cadmium level in cigarette smoker's blood is 3-4 time higher than for a non-smoker (Sun *et al.*, 2014). Sun *et al.*, 2014 conducted a study on 209 pregnant women living in Eastern China. They analyzed the lead, cadmium and selenium from umbilical cord blood, maternal urine and blood. They explained that the passive smoking might increase the concentration of cadmium in urine, but

it might not increase it in the maternal and umbilical blood. They suggested the possibility of crossing the placenta barrier, described in previous studies, that plays an important role in heavy metals accumulation (Ronco *et al.*, 2005). The dietary intake was not analyzed in this study but the authors suggested its importance. It is possible that selenium to have a protective role against cadmium. Menai *et al.* (2012) studied the cadmium effect on 901 pregnant women smokers and non-smokers from Western and Eastern France. Both studies had almost same baseline characteristics (e.g.: body mass weight index, baby birth weight, baby birth height). The median of cadmium concentration from maternal blood and cord blood in Menai *et al.* (2012) study were $0.8 \mu\text{g L}^{-1}$ and $0.5 \mu\text{g L}^{-1}$; in Sun *et al.*, 2014 study were $0.48 \mu\text{g L}^{-1}$ and $0.15 \mu\text{g L}^{-1}$. This made the cadmium from blood (according to Menai *et al.*, 2012) to be a biomarker for smoking toxicity in child development, knowing that the birth weight in the high-exposed to cadmium group was reduced by 204 g compared to the low-exposed to cadmium group.

Cadmium exposure was also studied to see if it is responsible for ADHD (attention deficit hyperactivity disorder) in children. The partial conclusions did not find it responsible for this, but future studies are necessary to prove the toxicity in children (Kim *et al.*, 2013). Cadmium from sea food and blood were not associated with Autism in Jamaica (Rahbar *et al.*, 2014).

Are the men smokers more affected than women smokers?

The answer at this question has many variables in the equation. There are factors like: number of cigarettes day⁻¹, type of cigarettes, life style, food type, age, working place, inhabiting environment (city/country side) and so one. There is no difference of cadmium presence in the blood for different age groups. There are studies that prove a higher cadmium level in woman than man blood, but there also are others with no significantly difference (Rambousková *et al.*, 2014). There are significantly differences between smokers and non-smokers like $1.29 \mu\text{g L}^{-1}$ and $0.53 \mu\text{g L}^{-1}$ (Rambousková *et al.*, 2014). Lin *et al.*, 2014 explained that the cadmium concentration in the blood samples from smokers (0.47 - $1.50 \mu\text{g L}^{-1}$) was 3 times higher than for a non-smoker (0.13 - $0.35 \mu\text{g L}^{-1}$). The population from a large city is more exposed to cadmium than the population from a smaller city (Rambousková *et al.*, 2014). This depends very much on the anthropogenic activities, population, economic factors and industrial development.

Damage of liver, kidneys and osteoporosis

Cadmium has been classified as a human carcinogen by IARC (International Agency for Research on Cancer) and US National Toxicology Program (Filipič *et al.*, 2012). It is rapidly transported by the blood to

several organs in the body. This quickly occurs after its absorption. It irreversibly accumulates in the kidneys, liver and lungs (Chang *et al.*, 2012). The kidneys have the central role in cadmium elimination from the body and they represent the first target of cadmium toxicity (Lin *et al.*, 2014). In Lin *et al.* (2014), cadmium from circulatory system was correlated with the risk of eGFR (estimated glomerular filtration rate) decreasing and albuminuria in the U.S. population aged 20 or older. The lower level of serum zinc was associated with the risk of reducing GFR. Zinc has an important protective role in cadmium toxicity. Its toxicity was associated with a high risk level of diabetes and diabetic nephropathy (Lin *et al.*, 2014). Most of the studies on neurotoxicity, hepatotoxicity and nephrotoxicity are conducted on models organism. Yuan *et al.* (2014) experimented on rats. Their aim was to study the oral acute exposure of rats to different concentrations $Pb(NO_3)_2$ - $CdCl_2$ for 14 days and sub-chronic oral toxicity for ninety days. Their results explained that the rat female were more sensitive than male to higher concentrations and the toxic effects were targeted on blood, kidneys, liver and testicles. The number of red cells from the blood was significantly decreased and the liver functions were reduced. Tsutsumi *et al.* (2013) run a study to observe if the rats exposure to Cd^{2+} modifies the plasma levels of S1P (produced by phosphorylation of sphingosine

kinases), LPA (lysophosphatidic acid), knowing that chronic exposure induces renal failure to fibrosis. On the other hand, cadmium induced injuries could not be directly applied to humans.

Chen *et al.* (2014) run a study on 321 individuals from China (202 women and 119 men). They suggested that a higher level of cadmium in blood is associated with a lower bone mineral density in women. The smoker's percentage in this study was below 5% and the study was limited because there were several variables that influence the bone mineral density, like diet. Kim *et al.*, 2014 conducted their study on 1086 (456 males and 630 females) living residents near a cooper refinery plant in Korea. The reported Cd^{2+} levels in urine were higher in female subjects (reported as $\mu g g^{-1}$ creatinine) than in male subjects. Their results suggested that an increased Cd^{2+} body burden in men directly decreased the bone mineral density which on contrary knowing that the female women are more exposed than man. The increased Cd^{2+} body burden in females firstly induced the renal microtubular damage and leads to osteoporosis. In Shin *et al.*, 2011 a total of 804 residents were surveyed from an industrial complex area in Korea. The aim of their study was to investigate the relationship between the bone mineral density and the urinary cadmium in different age groups for males and females. The authors concluded that females had a higher risk to osteopenia and

osteoporosis than males based on the relation urinary Cd^{2+} and bone mineral density. Osteopenia was associated with high concentration of urinary Cd^{2+} for females and males. The mineral density for children and adolescents (Age < 19) groups was not correlated with urinary Cd^{2+} and gender; the risk was not present at this age. Only the adult group had a significant correlation between these parameters, suggesting that the exposure period and age have the most important role (Shin *et al.*, 2012).

Is there any cure against cadmium exposure?

Tetraethylammonium salt of monesic acid – Ivanova *et al.* (2012) suggested that this compound can be used as treatment of subacute cadmium intoxication because tetraethylammonium salt of monesic acid is a good chelating agent. The general therapy with chelating agents is used for the treatment of acute and chronic metal intoxication. This compound was tested on mice. The cadmium level from kidneys and liver decreased with 50% comparative with the control group consequent to the treatment. The testing group was treated during the 15th day of the 28 experiment days with 16 mg/body weight.

Soybeans diet– Díaz Matías *et al.* (2013) used male Wistar rats in an experiment with tap water contaminated with CdCl_2 (15 and 100 ppm Cd^{2+}). Two types of diet were analyzed in this experiment: one with casein and one with soybeans. The

authors concluded that the soybeans diet may provide benefits as an antioxidant in prevention of arterial injuries caused by cadmium exposure in experimental conditions. It is possible to protect the aorta against the cadmium toxicity.

Caffeic acid phenethyl ester– Kobroob *et al.* (2012) studied on Wistar rats the role of this compound in kidney mitochondria protection. This is an active component of the propolis from honeybee. In the first part of their study the authors showed that cadmium was responsible for kidney mitochondrial dysfunction by producing the oxidative stress in isolated mitochondria groups incubated with 10, 20, 30 and 40 μM CdCl_2 . The results presented the antioxidant potential of caffeic acid phenethyl ester in kidney mitochondrial protection against the renal toxicity caused by cadmium.

Litchi chinensis Sonn.(litchi) flower extract – Hwang *et al.* (2013), observed on rat liver cells treated with CdCl_2 that litchi flower extract had an active antioxidant effect against cadmium toxicity in liver by decreasing the oxidative damage and the TGF- β 1 in HSCs activation.

Allium cepa L.(common onion) extract–Ige and Akhigbe (2013) run an experiment on male Wistar rats to analyze if the common onion extract is a possible remedy for cadmium exposure. The rats that were under Cd^{2+} exposure received contaminated drinking water with CdSO_4 (1.5ml/kg body weight from 0.3mg $\text{ml}^{-1}\text{CdSO}_4$).

Onion extract (1 ml/100 g body weight) was administrated to the treatment group. The authors firstly demonstrated cadmium toxicity: damage in vascular function, hemorheology, dyslipidaemia and oxidative stress. The onion extract was a good protector against atherosclerotic condition *via* a mechanism depending on lipid peroxidation induced by cadmium. It was considered to have applications in the treatment of atherosclerosis and hypertension induced by Cd²⁺.

Procyanidin extract from grape seed—Chen *et al.* (2013) tested on Kunming mice the beneficial effect of procyanidin extract against renal damage (oxidative damage, renal apoptosis related genes Bax and Bcl-2) produced by cadmium. The authors used for Cd²⁺ exposure the concentration of 5mg/kg body weight CdCl₂ for all groups, orally administrated. The groups were treated with procyanidin extract in different doses (50, 100 and 200mg/kg body weight). The higher dose of procyanidin extract had a protective effect against Cd²⁺ in renal oxidative damage and reduced the renal apoptosis by interfering with Bax and Bcl-2 expression.

Epigallocatechin-3-gallate from green tea – Abib *et al.* (2011) analyzed the protective role of epigallocatechin-3-gallate in brain mitochondria obtained from Wistar rats against neurotoxicity of Cd²⁺. The samples were incubated with CdCl₂ (100, 200 or 300 μM) and epigallocatechin-3-gallate (10, 50 or

100 μM). The results explained the protective effect of epigallocatechin-3-gallate against metabolic dysfunction and lipoperoxidation in brain mitochondria from rat brain caused by Cd²⁺ neurotoxicity. This compound proved important antioxidant and chelating properties in this experiment. The future of epigallocatechin-3-gallate as treatment against Cd²⁺ neurotoxicity is not far away, but there are required more *in vivo* exams and pharmacological studies.

Chlorpromazine and verapamil— the study was done by Xu *et al.* (2008) on Wistar rats *in vivo* experiment. The authors intraperitoneally injected CdCl₂ (7μM/kg body weight/day) and different concentrations of chlorpromazine and verapamil. They studied the toxicity of cadmium in kidneys. These two compounds reduced the kidneys damage caused by cadmium (oxidative damage; Ca²⁺ intracellular disturbance of homeostasis; abnormal activation of PKC, Na⁺-K⁺-ATPase and Ca²⁺ATPase). Chlorpromazine and verapamil reduced the oxidative stress and stabilized calcium homeostasis.

Succimer chelation— Cao *et al.* (2013) studied the cadmium exposure in children from US. They observed the succimer treatment against the cadmium poisoning because it was approved for pediatric lead poisoning. The studies run on animals provided positive effects in reduction of cadmium absorption and protection of the organism against it. According to

this study results, after orally administration of the treatment, the cadmium level from the children blood was slightly increased. The succimer did not reduce the cadmium level. Cadmium once entered in the cells, binds to different compounds and is hard to eliminate it in cases of Cd^{2+} poisoning.

Cadmium in birds

The level of cadmium in birds is important to analyze the environmental health. Birds are very sensitive to environmental changes and pollutants. The satellite monitoring system of bird's populations provided information about their routes, feeding and reproduction places. The researcher can measure anthropogenic impact better and better. The studies can be done in laboratory conditions and by observation in nature. Toxicological studies conducted in laboratory conditions provide fast and clear results about the toxicity of a compound, but they are limited: they cannot be replicated with all environmental and food conditions. There are many possible interactions which are not correlated and cannot be replicated (Burger *et al.*, 2008). Toxicological observations in nature and analyzes are closer to reality but are extremely complicated and restricted by many interactions such as: environment-chemistry-organism, organism-organism, organism-biochemical processes inside the body. Toxicological results from free living

animals are not similar to those from experimental conditions which are clearer (Burger *et al.*, 2008).

Binkowski *et al.* (2013) analyzed liver and kidney samples from *Anas platyrhynchos* L. (Mallard) and *Fulicaatra* L. (Coot). The birds were legally collected by hunters in 2006-2008 during hunting seasons near Zator in Poland. The study was focused on lead and cadmium concentrations and lesions from liver and kidneys. Most exposed to lead and cadmium were the mature birds; they had more liver and kidneys lesions than juveniles. Some specimens were more intoxicated with lead than with cadmium. The conclusions did not recommend consumption of mallards and coots from Zator area because the concentrations of these metals were over the limit accepted by European safety norms. Binkowski and Sawicka-Kapusta (2015) used same species to study the cadmium distribution for mallards and coots collected from Zator and Milicz, Poland. The birds were legally collected by hunters in 2006-2009, during the hunting seasons. There were analyzed samples from: feathers, bones, muscle, brain, spleen, liver, kidneys, blood, gizzard content and excrements. Their results generally showed that cadmium concentration in kidneys>liver>spleen>brain>muscle>bone>feather for both studied species. The authors observed that the mallards and coots from Zator area were more affected by Cd^{2+} than the ones from Milicz. The *in vivo* biomarkers

(feathers, blood and excrements) had not significant results in order to conclude in their study.

Mallory *et al.* (2014) studied the hepatic cadmium and zinc in *Somateria mollissima* L.(common eider) from three Canadian colonies. They selected for the study females of common eider. The birds were euthanized by cervical dislocation. This avoids any possible contamination. The samples collected in 2008 were analyzed and compared with the results from 1992-1993 and 2001-2002. This study was very important for the cadmium monitoring in the Arctic area. The concentrations of cadmium in liver were: $8.23 \pm 3.03 \mu\text{g g}^{-1}$ in 1992-1993, $15.70 \pm 3.93 \mu\text{g g}^{-1}$ in 2001-2002 and $44.67 \pm 18.82 \mu\text{g g}^{-1}$ in 2008. This study represents a warning message regarding the changes occurred in the arctic marine ecosystems and the contamination of the food webs with cadmium.

There were reported *in vitro* experiments proving that cadmium and lead decreased the number of erythrocytes and induced the apoptosis of the blood cells from *Anas platyrhynchos* L. (Mallard) and *Buteo buteo* L. (Common buzzard) (Romero *et al.*, 2009; Hernández-García *et al.*, 2014). In laboratory conditions, Cadmium caused malformations of chicken at early stages of development and DNA methylation in hens (Zhang *et al.*, 2009; Yamamoto *et al.*, 2012). Chicken embryos are model organisms in the study of cadmium genotoxicity and different organs development.

We presented in this study a few problems caused by cadmium in humans and other life forms with the answers based on the scientific work made by researchers all around the world to whom we are grateful. There are many questions without an answer about cadmium toxicity and possible diseases that may be caused in humans' bodies and others life forms. This metal in high concentrations has a negative impact and it is a problem for now and in the future. Even if the pollution sources are stopped; - what will it happen with the cadmium entered in the food webs? Should we be afraid of this element? The answers at this final question will be different for each person, but it is necessary to know the exposure risk and sources.

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