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CADMIUM POISONING WITH ANALYTICAL ASPECTS AND ITS MANEGEMENT

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ABSTRACT

Cadmium is a minor metallic element present naturally in the earth crust and water. Toxicity caused by cadmium compounds is not common. The routes of exposure are by inhalation of cadmium fume, ingestion and through smoking. Toxicity is mainly accidental through food stuffs, cigarette smoking and occupational. It primarily causes oxygen-stress to the tissue forming free oxygen radicals. The main organs involved are liver, kidneys and lungs but it also involves other organ systems too and cause 'ouch-ouch disease'. Cadmium also alleged to be carcinogen. Management of the cadmium poisoning is done in the same line as any other heavy metals, with gastric lavage and chelating agents.

Key words: Cadmium, Poisoning, Ouch-Ouch Disease, Itai-Itai Disease, Treatment, Prevention.

INTRODUCTION

Cadmium is a naturally occurring components in the earth's crust and waters, and present everywhere in our environment. It is a soft, can cut with a knife, malleable, ductile, bluish-white, divalent metal. It is soluble in acids but not in alkalis and water. As a bulk metal, cadmium is not inflammable, however, in powdered form it may burn and release toxic fumes. It emits a characteristic brown non-irritating fume on heating and thus does not alarm the exposed individual. It is resistant to corrosion and acts as a protective layer when deposited on other metals.

Cadmium is used as a barrier to control nuclear fission, as it has the ability to absorb neutrons. Because of their unique physical, mechanical, and electrochemical properties, cadmium metal and a few other cadmium compounds such as cadmium sulphide, cadmium oxide and cadmium hydroxide are used in pigments, coatings, stabilizers, specialty alloys and electronic compounds, but it is mostly used in rechargeable nickel-cadmium batteries. Cadmium pigments are more stable than organic colouring agents at high temperatures and are not easily degraded by light. Cadmium pigments are widely used in thermoplastics, ceramics, glazes, and artists' colours.

Sources of Cadmium [1,2]

- Cadmium is found throughout the environment from natural sources and processes like erosion and abrasion of rocks and soils, forest fires, volcanic eruptions and in water.
- Generally it is recovered as a byproduct from zinc concentrates and spent nickel cadmium batteries.
- It is also found in manures and pesticides and foodstuffs like liver, mushrooms, shellfish, mussels, cocoa powder and dried seaweed.

Exposure of Cadmium [1,2]

- Human uptake of cadmium is mainly through food.
- Smoking causes a higher exposure to cadmium.

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- People who live near hazardous waste sites or factories that release cadmium into the air and who work in the metal refinery industry.
- During production of artificial phosphate fertilizers.
- Occupational exposure to cadmium is through inhalation of fine dust and fumes.
- Cadmium is also found in some industrial paints and may represent a hazard when sprayed.
- In Japan, environmental exposure to cadmium has been particularly problematic where many people have consumed rice grown in cadmium contaminated irrigation water. This phenomenon is known as itai-itai **(**ouch-ouch**)** disease.
- In February 2010, cadmium was found in an entire line of Wal-Mart exclusive Miley Cyrus jewellery. The charms were tested and were found to contain high levels of cadmium. Wal-Mart did not stop selling the jewellery until May 12 because it would be too difficult to test products already on its shelves [3].
- Cadmium was detected in the paint used on promotional drinking glasses for the movie Shrek Forever after, sold by McDonald's Restaurants, triggering a recall of 12 million glasses.

Environmental Effects of Cadmium [1]

A very large amount of cadmium is released naturally into the environment, about 25,000 tons a year. About half of this cadmium is released into rivers through weathering of rocks and into air through forest fires and volcanoes. Cadmium is released through human activities, such as manufacturing. Cadmium waste streams from the industries mainly end up in soils. Cadmium waste streams may also enter the air through (household) waste combustion and burning of fossil fuels.

Another important source of cadmium emission is the production of artificial phosphate fertilizers. Cadmium can be transported over great distances when it is absorbed by sludge. This cadmium-rich sludge can pollute waters as well as soils. Cadmium strongly adsorbs to organic matter in soils. Acidified soils enhance the cadmium uptake by plants. This is a potential danger to the animals that are dependent upon the plants for survival. Earthworms and other essential soil organisms are extremely susceptive to cadmium poisoning and when cadmium concentrations in soils are high they can influence soil processes of microorganisms and threat the whole soil ecosystem.

In aquatic ecosystems, cadmium can bio accumulates in mussels, oysters, shrimps, lobsters and fish. The susceptibility to cadmium can vary greatly between aquatic organisms. Freshwater organisms are known to be more susceptible to cadmium poisoning than salt-water organisms.

Cadmium has no known useful role in higher organisms, but a cadmium-dependent carbonic anhydrase has been found in some marine diatoms. The diatoms live in environments with very low zinc concentrations and cadmium performs the function normally carried out by zinc in other anhydrases [4,5]

Human Intake of Cadmium [6]

Human intake of cadmium is either by ingestion or inhalation. Skin absorption is not significant. Only about 2-6% ingested cadmium is absorbed. Factors influencing cadmium absorption are mainly the cadmium compound present in the food and the iron status of the exposed individual.

In contrast, from 30% to 64% of inhaled cadmium is absorbed by the body, depending upon the chemical form, solubility and particle size.

Cigarettes smoking cause 50% cadmium level in the body. On average, smokers have 4–5 times higher blood cadmium concentrations and 2–3 times higher kidney cadmium concentrations than non-smokers. Passive smoking has little effect.

PHARMACO-KINETICS OF CADMIUM

Mechanism of action

Cadmium works as a catalyst for the formation of reactive oxygen species and increases oxygen stress. It increases lipid per oxidation and depletes glutathione and protein-bound sulfhydryl groups. It also stimulates the production of inflammatory cytokines and down-regulates the protective function of nitric oxide formation.

Cadmium expresses genotoxic activities in vitro in cells and in vivo in animals; but there is limited evidence for human genotoxicity. Cadmium causes mutations, breaks DNA strand and damages chromosomes, and also causes cell transformation and impairment in the process of DNA repair in cultured mammalian cells. Cadmium modulates gene expression and signal transduction.

Cadmium metal and cadmium compounds, such as cadmium chloride, oxide, sulfate, and sulfide, are carcinogenic in animals. In animals, increased rates of testicular, prostate, and lung cancer have been described. In humans, epidemiological evidence shows a small increase in the relative risk of lung cancer in workers exposed to cadmium and cadmium compounds.

In acute exposures, the relatively more soluble cadmium chloride, cadmium oxide fume, and cadmium carbonate compounds are more toxic than the relatively less soluble cadmium sulfide compounds. This difference is mainly due to higher lung absorption and retention times for the more soluble compounds. Less soluble pigments are removed by muco-ciliary action. However, the toxicity does not strictly correlate with solubility, and that solubility of cadmium oxide in biological fluids may be greater than its solubility in water.

Inhalation involve mainly lungs causing local irritation and inhibition of alpha1-antitrypsin associated with emphysema.Oral ingestion mainly involves kidneys

and causes proximal tubular injury leading to proteinuria associated with beta 2-macroglobulin.

Chronic exposure can lead to various CNS symptoms as olfactory dysfunction by working on amygdala. Cadmium taken up in amygdalar neurons may be released from the neuron terminals, and affect the degree and balance of excitation-inhibition in synaptic neurotransmission [7].

Metabolism of cadmium

The major route (98%) of cadmium intake for the non-smoking and non-occupationally-exposed population is through ingestion of food and water. If smoked, tobacco smoke transports cadmium into the lungs. Blood transports it through the rest of the body.

When ingested, Cadmium is first transported to the liver through the blood. Liver bounds it to the protein and form complex and then transported to the kidney. Here it accumulates in the renal cortex and causes proximal renal tubular dysfunction.

Cadmium accumulates mainly in the renal cortex and liver. The pancreas, thyroid, gall-bladder, and testes can also contain relatively high concentrations. Accumulation of cadmium occurs as the age increases. Cadmium accumulates with age until a maximum level is reached at about age 50, the total body burden of a person of 50 years of age ranges from 5 to 40 mg. About half the body burdens is found in the kidneys and liver [8].

Cadmium binds to red blood cells, plasma albumin, and metallothionein. Metallothionein may serve as a barrier to protect the fetus; but in cases of excessive maternal exposure some cadmium will cross the placenta.

Cadmium is initially detoxified in the liver through the formation of a metallothionein-cadmium complex, which is slowly released from that organ. However, cadmium-metallothionein complex can be nephrotoxic as it accumulates in the kidneys.

Most cadmium that is ingested is excreted in the feces. Most absorbed cadmium is excreted very slowly through urine and faeces. Cadmium is also eliminated through hair and breast milk but not much significance. It can cross placenta, though partially and fetal exposure can occur [10].

Onset and Duration of Action

Biological half-time of cadmium is extremely long. In human kidney half-life ranges between 6 and 38 years and in human liver between 4 and 19 years [9].

Fatal Dose and Fatal Period [10]

An exposure of 2,500 minutes X mg/m^3 of cadmium in air would be fatal. Ingestion of >100 mg of its soluble salt can be lethal. Cadmium's lethal effect is different among the chemical forms in the following order from most to least toxic: cadmium chloride > cadmium sulfate ≈ cadmium oxide dust > cadmium sulfide. Time to death after cadmium iodide ingestion is 7 days [11] and, 33 hours after ingestion of the cadmium chloride [12].

CLINICAL FEATURES/SYMPTOMS [13,14]

Major route of entry of cadmium is through ingestion of food and through inhalation of smokes. Cadmium tends to accumulate in the human body with 33% in the kidneys and 14% in the liver. The main problem with cadmium in humans appears to be that the body seldom excretes as much cadmium as is absorbed.

Inhalation: Onset of symptoms is usually delayed for 4 to 10 hours. In high acute exposures, the initial symptoms are respiratory distress but the symptoms do not occur following lower-level, longer-term inhalation exposures. Longer-term occupational exposure to low levels of cadmium, however, has been reported to cause emphysema and dyspnea in humans.

Acute exposure to cadmium fumes may cause flu like symptoms including chills, fever, and muscle ache, which are sometimes referred to as "the cadmium blues". Acute inhalation may also cause symptoms similar to those of metal fume fever. Symptoms may resolve after a week if there is no respiratory damage.

Acute cadmium poisoning has occurred following exposure to fumes during the melting or pouring of cadmium metal [15]. Acute pneumonitis resulted from inhalation of concentrations between 0.5 and 2.5 mg/m^3 for 3 days.

Fatalities have resulted from a 5h exposure to 8 mg/m^3, although some individuals have recovered after exposure to 11mg/m^3 for 2h.

More severe exposures can cause tracheo-bronchitis, pneumonitis, and pulmonary edema. Symptoms of inflammation may start hours after the exposure and include cough, dryness and irritation of the nose and throat,headache, dizziness, weakness, fever, chills, and chest pain.

Cadmium may accelerate the development of emphysema in smokers. Inhaling cadmium-laden dust quickly leads to respiratory tract and kidney problems which can be fatal (often from renal failure), which may progress into complete Fanconi syndrome with decreased tubular reabsorption of proteins, glucose, amino acids, calcium, phosphorus and with decreased ability to acidify & concentrate the urine.

Chronic exposure to airborne cadmium results in a number of toxic effects; the two main symptoms are lung emphysema and proteinuria. Emphysema appears after approximately 20 years of exposure.

Ingestion: The most common way of acute cadmium poisoning through ingestion is consumption of acidic food or beverages, which are improperly stored in containers with a cadmium glaze. Ingestion of any significant amount of cadmium causes immediate poisoning and damage to the liver and the kidneys. In high doses, it irritates the gastric epithelium. The symptoms of severe cadmium ingestion are nausea, vomiting, abdominal cramps and pain, diarrhea, and tenesmus. Cadmium causes impaired absorption of iron from the diet leading to anemia. Chronic exposure leads mainly to nephrotoxicity.

SYSTEMIC EFFECT ON BODY

Cardio-vascular system: Inhalation exposure does not have any significant effect on the cardiovascular system. In some studies, the mortality from cardiovascular disease was found lower in the cadmium-exposed population.

Gastrointestinal system: Symptoms mainly includes pain or tenderness at the epigastrium associated with nausea and some constipation.

Hematological system: Cadmium-induced anemia primarily results from impaired absorption of iron from the diet following gastrointestinal exposure to cadmium. The amount of gastrointestinal exposure following cadmium inhalation is variable depending on the form and dose.

Musculoskeletal system: Calcium deficiency, osteoporosis, or osteomalacia can develop after long-term occupational exposure to high levels of cadmium. Effects on bone generally arise only after kidney damage has occurred and are likely to be secondary to the resulting changes in calcium, phosphorus, and vitamin D metabolism.

Hepatic: Liver effects are mainly associated with ingestion of cadmium. Cadmium accumulates in the liver as well as the kidney. The resistance of the liver to toxic effects of cadmium may be related to a higher capacity of the liver to produce metallothionein that binds to cadmium and lowers the concentrations of free cadmium ions.

Renal: Kidney is the main target organ of cadmium toxicity following inhalation of cadmium leading to proteinuria and a decrease in glomerular filtration rate. One of the first signs of kidney effects is tubular dysfunction characterized by an increased urinary excretion of low-molecular-weight proteins such as β2-microglobulin, human complex-forming glycoprotein (pHC) (also referred to as α1-microglobulin), and retinol binding protein or increased urinary levels of intracellular enzymes such as N-acetyl-β-glucosaminidase (NAG). At higher exposure levels, urinary levels of high-molecular-weight proteins such as albumin increase.

Chronic exposure to very high cadmium levels can result in glomerular damage resulting in decreases in glomerular filtration rate (GFR). Due to disruption of calcium metabolism as a result of kidney damage, there is increased frequency of kidney stone formation in cadmium workers. Cessation of exposure does not generally result in a reversibility of kidney damage. The initial level of retinol binding protein is the most important determinant in reversibility of tubular proteinuria and that the influence of urinary cadmium level or length of time since exposure cessation is not statistically significant.

Central nervous system: Cadmium rarely penetrates through blood brain barrier; however chronic exposure can lead to various CNS symptoms such as olfactory dysfunction and many associated symptoms like headache and nausea.

NORMAL/ REFERENCE VALUES

The current reference range for acceptable blood Cadmium concentrations in healthy persons is less than 1µg/L and toxic level is more than 1µg/L (Table 1).

Biomarkers [9]

The urinary beta-2 microglobulin test is an indirect method of measuring cadmium exposure. Blood or urine cadmium concentrations provide a better index of excessive exposure in industrial situations or following acute poisoning, whereas organ tissue (lung, liver, and kidney) cadmium concentrations may be useful in fatalities resulting from either acute or chronic poisoning. Cadmium concentrations in healthy persons without excessive cadmium exposure are generally less than 1µg/L in either blood or urine. Diagnosis is based upon:

(1) History of exposure

(2) Serum cadmium levels will help confirm the diagnosis, but it does not correlate with the severity of intoxication. It should not be used to determine the need for treatment

DIFFERENT INVESTIGATION IN CASE OF CADMIUM POISOINING

Urinary β2-microglobulin: In healthy, unexposed persons, β2-microglobulin levels average about 200µg/g creatinine. Excretion increases with age and cadmium exposure. In cadmium workers, urine levels greater than 300µg/g creatinine indicate possible early kidney disease.

Urinary Retinol Binding Protein (RBP): RBP is a low molecular weight (LMW) protein found in the urine after chronic cadmium exposure. However, it only shows decrease tubular reabsorption due to any cause, therefore, it should only be used as a confirmatory test in cases of suspected cadmium exposure.

Urinary metallothionein, MTN: Urinary levels of MTN correlate well with urinary cadmium levels and can reflect total cadmium body burden; but as once renal dysfunction has developed, urinary concentration of the cadmium-MTN complex increases significantly.

The other markers have been assessed and shown to have significant association with cadmium exposure as:
- Albumin in urine;
- N-acetyl-D-glucosaminidase (NAG) in urine;
- Urinary transferrin;
- Most tubular antigens.

Chest X-rays are also useful in detecting cadmium poisoning.

CHEMICAL TEST OF CADMIUM POISONING

1. Qualitative Test (Colour/Spot test)

Hydrogen Sulphide test

1. One ml of acidic solution of extract is taken in a test tube.
2. Hydrogen sulphide gas is passed through it.
3. Yellow precipitate of cadmium sulphide is observed which is soluble in hydrochloric acid but insoluble in ammonia.

Potassium cyanide test

1. One ml of extract is taken in a test tube.
2. Few drops of potassium cyanide solution are added to it.
3. White precipitate is observed which indicates the presence of cadmium.

Dinitro-P-Diphenyl Carbazide test

1. A drop of ammonical extract is taken on a spot tile.
2. A drop of sodium hydroxide followed by a drop of potassium cyanide solution is added to it.
3. Few drops of dinitro-P-diphenyl carbazide solution followed by formaldehyde solution are added to it.
4. Brown precipitate is observed which rapidly changes to greenish blue, indicates the presence of cadmium.

Nitronapthalene – di-azo-amino azo-benzene test

1. A drop of acidified solution containing few drops of sodium potassium tartrate solution is added to it on a Whitman paper.
2. A drop of potassium hydroxide solution is added to it.
3. A bright-pink spot surrounded by a blue circle is observed which indicates the presence of cadmium.

Various kits are now available for diagnosis of cadmium toxicity, cadmium level in water at home which can measure cadmium levels in parts per million (as osumex cadmium test kit).

2. Quantitative Test

1. Determination of Cadmium in blood by atomic absorption spectrophotometry

Standard Cadmium Solution: 2.7442 gm. of cadmium nitrate is dissolved in sufficient 1 M nitric acid to produce 1000 ml. It is serially diluted with a 0.05% solution of nitric acid to produce solutions containing 0.0005, 0.001, 0.002, 0.004, 0.006, 0.008 and 0.01µg/ml.

Analysis

1. 100 µl of the sample of whole blood 100 µl of a 0.05% solution of nitric acid and 100 µl of a 1% solution of ammonium hydrogen phosphate are added and mixed thoroughly.
2. 20 µl. of the mixture is introduced into the graphite furnace.
3. The drying, ashing and atomization are made.
4. The absorbance is recorded at 228.8 nm.
5. The procedure is repeated using in place of sample, solutions prepared by adding 100 µl of each of the diluted standard solutions to 100 µl quantities of pooled normal blood.
6. The absorbance of each of standard solutions is plotted against the concentrations of cadmium.
7. The concentration of cadmium in the sample is read off from the calibration curve.
8. The graph should be linear in the range 0 to 0.01µg/ml.

2. Voltammetric analysis of Cadmium (Cd) in blood and urine.

The electrode is washed well with milli Q water. 10 ml milli Q water, 1ml Ammonium Acetate buffer is taken in voltammetric vessel and voltammograms of blank is recorded under the voltammetric conditions given in the Table 2, with peak potential of cadmium as -560mV. After completion of blank voltammograms, 0.1ml of digested sample is added in voltammetric vessel and voltammograms is recorded. After completion of sample voltammograms, 0.1ml of 1ppm standard solution of Cadmium is added and voltammogram is recorded. Again, 0.1ml of 1 ppm standard solution is added in same vessel and voltammogram is recorded second time. The voltammogram of sample, standard for Cd is given in Fig 1. Extrapolation graph which gives the value of amount for Cd is given in Fig 2.

MANAGEMENT / TREATMENT OF CADMIUM POISIONING

Pre-hospital management [6]

1. When inhaled, take the person to fresh air, rest in a half upright position. If indicated provide artificial respiration and referred for medical attention.
2. If ingested, provide him rest and is referred for medical attention.
3. When exposure is through skin, remove all contaminated clothes. Rinse and then wash skin with water and soap.
4. When eyes are exposed, rinse with plenty of water for several minutes (remove contact lenses if easily possible) and referred for medical attention.

Hospital management/treatment [6]

For Acute High-dose Exposure:The mainstay of management for most inhalation exposure victims is supportive treatment including

1. Fluid replacement,
2. Supplemental oxygen, and
3. Mechanical ventilation.
4. In cases of ingestion, soon after exposure gastric decontamination by emesis or gastric lavage may be beneficial. Administration of activated charcoal is not effective.

For Chronic Exposure : The mainstay of management includes:

1. Remove from exposure sources:For chronic poisoning victims, the most important intervention is prevention of further exposure.

2. Chelation therapy: Cadmium has a high affinity for the metal-carrying protein metallothionein, so the chelation of cadmium is very difficult. Chelation therapy should not be performed and all treatment is supportive. Hydration and the correction of hypokalaemia are the main therapies. Haemodialysis may be used to remove circulating cadmium from the bloodstream, although the literature on the subject is scarce. Addition of a chelating agent during haemodialysis, particularly Ethylene-di-amine Tetra-acetic Acid (EDTA), will increase the amount of cadmium removed by the dialysate. 2,3dimercaptopropanol (BAL)-Cadmium complex is extremely nephrotoxic and therefore is not used.

3. Encourage patient to eat foods rich in calcium, iron, protein, and zinc.

The prognosis depends on the nature and severity of the cadmium load. Most cases of mild exposure resolve spontaneously after a few days. However, in other cases, cadmium can lead to permanent damage with shortened lifespan, or even death.

Preventive measures in the workplace, is must, which include

- Improvement of ventilation by opening windows,
- Installing or running an exhaust fan or a mechanical ventilation system, and
- Using proper personal protective equipment such as respiratory protection, protective clothing, eye protection, and gloves.
- Important hygienic measures, that are the first line of defence, include:
- A clean work area free of dust,
- Showering and changing clothes immediately on completion of work in the jewellery area,
- Disposing of the contaminated clothing at the work site,
- Not smoking, eating or drinking in the work area, and
- Washing hands well before smoking, eating, or drinking after work or during breaks.

Figure 1. Voltamogramme of Cd , A) 0.1 ml sample in 1ml acetate buffer (pH 4.6) + 10 ml milli Q water, B) A + 0.1 ml standard solution of Cd(1 ppm), C) B + 0.1 ml standard solution of Cd(1 ppm).

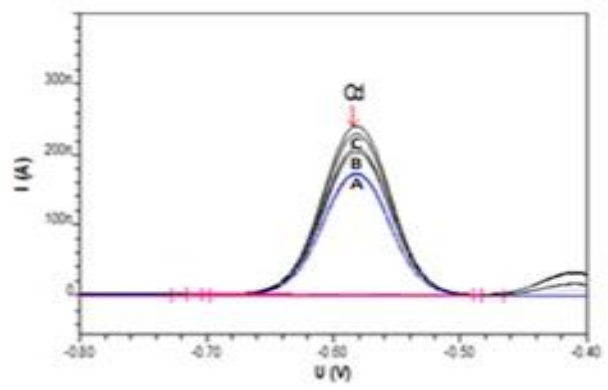

Figure 2. The extrapolation curve of Cd obtained from standard addition technique.

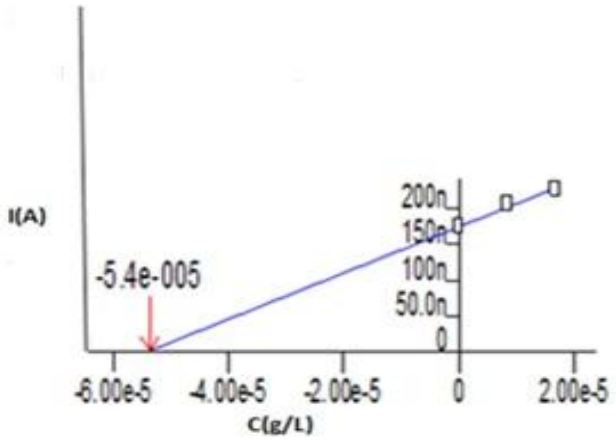

Table 1. Normal and Toxic level of Cadmium

Matrixes	Normal level	Toxic level
Blood	<1µg/l	>5µg/l
Urine	<1µg/l	>5µg/l

Table 2. Voltammetric conditions for the analysis of Cd

S.N	Parameters	Description	S.N	Parameters	Description
1	Auxiliary electrode	Pt	12	Stripping	Anodic
2	Reference Electrode	Ag/AgCl, 3M KCl	13	No of replications	2
3	Working electrode	MME (HMDE)	14	Sweep rate	60 mV/s
4	Calibration method	Standard addition	15	Deposition time	90 s
5	Deposition potential	-1150 mV	16	Equilibration time	10 s
6	Drop size	4	17	Pulse amplitude	50 mV
7	Stirrer speed	2000 rpm	18	Start potential	-1150 mV
8	Mode	Differential pulse (DP)	19	End potential	100 mV
9	Initial purge time	300 s	20	Voltage step	6 mV
10	Addition purge time	10 s	21	Peak potential Cd^{2+}	-560mV

DISCUSSION AND CONCLUSION

All the working places where cadmium fumes may be formed should be well ventilated. Ground water and soil should be checked for cadmium. Cadmium-coated containers should be avoided and should never be used with acidic liquids such as fruit juices. Coal and oil-burning utilities should be monitored for cadmium discharge. Nickel-cadmium batteries should be recycled or disposed of as toxic waste.To help reduce the cadmium toxicity, following steps are important:

1. No smoking as smoking is the single most important source of cadmium intake for most persons.
2. Identification of potential sources of cadmium in and around home, at work, and where children play.
3. All the fertilizers should be tested for cadmium. Some fertilizers have been found to be high in cadmium, which may then concentrate in the vegetables. Avoid any use of cadmium containing fungicides near vegetable gardens.
4. Read instructions for safely using cadmium-containing fungicides or fertilizers on lawn or garden.
5. Balanced diet that provides enough calcium, iron, protein, and zinc.
6. Proper placing of cadmium containing compounds at home.
7. Keep nickel-cadmium batteries out of the reach of small children and ensue their proper disposal/recycle.
8. Have well water tested for the presence of cadmium and if cadmium is present in well water, consider using bottled water for drinking or install a water filter that removes cadmium and other metals from drinking water.
9. Avoid bringing cadmium home on clothing, skin, hair, tools, or other objects while working around cadmium.
10. Barr young children to play in or around hazardous waste sites.

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