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Neurotoxic Heavy Metals in the Human Brain - II. The Cadmium - Alzheimer Connection

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Abstract

Cadmium is a neurotoxicant in humans, although its evidence is still limited. Exposure to this heavy metal is linked to accelerated cognitive decline and an increased risk of Alzheimer's disease and related dementias. It acts as a neurotoxin that accumulates in the brain, promoting oxidative stress, inflammation, and key Alzheimer pathologies like amyloid-β plaques. Chronic exposure is associated with higher mortality, particularly in those individuals with genetic risks. While evidence supporting the link between Cadmium exposure and Alzheimer's is growing, some studies have noted that results can be sensitive to factors but require further research to fully understand the relationship. Considered in this article are sources of exposure to Cadmium; its production, uses, and releases to the environment; environmental effects; transport to the brain and into neuronal cells; and the experimental evidence linking Cadmium to Alzheimer's disease. The associated neurotoxicity will be examined as well as its health effects in the brain and more generally in various body organs. The elements of diagnosis will be set forth as well as the various treatment approaches of Cadmium poisoning. Lastly, the special case of Cadmium chloride will be detailed.

Abbreviations

Aβ: Amyloid-beta; AD: Alzheimer's disease; ADRD: Alzheimer's disease and related dementias; ALS: Amyotrophic lateral sclerosis; ATSDR: (U.S.) Agency for Toxic Substances and Disease Registry; β2M: Beta-2 microglobulin; BAL: British anti-Lewisite; BBB: Blood-brain barrier; BCSFB: Blood-cerebrospinal fluid barrier; Cd-B: Blood-CD; Cd-U: Urinary-Cd; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CNS: Central nervous system; CNT: Carbon nanotube; COPD: Chronic obstructive pulmonary disease; CSF: Cerebrospinal fluid; DMSA:

Dimercaptosuccinic acid or succimer; DPA: Penicillamine; DTPA: Dimethyl triamine pentaacetate; ECD: Edetate calcium disodium; EDTA: Ethylenediaminetetraaceric acid; EPA: (U.S.) Environmental Protection Administration; E.U.: European Union; GIT: Gastrointestinal tract; HEPA: High efficiency particulate air; IARC: International Agency for Research on Cancer; ICA: International Cadmium Association; IQ: Intellectual quotient; MMSE: Mini-Mental State Examination (or Folstein test); MND: Motor neuron disease; NAC: N-acetyl cysteine; NES: Neurobehavioral evaluation system; NFT: Neurofibrillary tangles; NHANES: (U.S.) National Health and Nutrition Examination Survey; NIA: (U.S.) National Institute of Aging; NTHM: Neurotoxic heavy metal; ONS: Olfactory nervous system; OS: Oxidative stress; OSHA: (U.S.) Occupational Safety and Health Administration; PAD: Peripheral artery disease; PD: Parkinson's disease; PPE: Personal protective equipment; QD: Quantum dot; ROS: Reactive oxygen species; SPECT: Single photon emission computed tomography; UNEP: United Nations Environmental Program; USGS: (U.S.) Geological Survey; WHO: World Health Organization: XRF: X-ray fluorescence.

Chemical elements: Ag: Silver; Al: Aluminum; Al2O3: Aluminum oxide; As: Arsenic; Ca: Calcium; Cd: Cadmium; CdCl2: Cadmium chloride; CdSe: Cadmium selenium; CdTe: Cadmium telluride; Cu: Copper; Fe; Iron; Hg: Mercury; Mn: Manganese; NAC: N-acetyl cysteine; Ni: Nickel; NiCd: Nickel cadmium; Pb: Lead; Se: Selenium; T2O3: Titanium oxide; Zn: Zinc; ZnO: Zinc oxide; ZnS: Zinc sulfide.

Drugs cited:

Dimercaprol; Dimethyltriaminepentaacetate; Dithiocarbamate. Ethylenediaminetetraaceric acid; Penicillamine.

Diseases mentioned: Alzheimer's disease; Amyotrophic lateral sclerosis; Cancer; Chronic obstructive pulmonary disease; Itai-Itai disease; Metal fume fever; Motor neuron disease; Osteoporosis; Parkinson's disease; Peripheral artery disease; Proteinuria; Pulmonary edema.

Keywords

Alzheimer's disease; Cadmium; Chelating agents; Cognition; Decontamination; Memory impairment; Nanoparticles; Neurotoxicity; Poisoning.

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Cadmium (Cd) is a bluish silvery, soft, ductile heavy metal that, in virtually every form, is very toxic and harmful to the environment with no essential physiologic function in humans. It is classified as a Group-I carcinogen by the International Agency for Research on Cancer (IARC). Long-term exposure to low-level Cd increases risks for diabetes, hypertension, kidney damage, lower lung function, and osteoporosis (Figure 1).

Figure 1: The Cadmium metal

Recently, Cd has emerged as a neurotoxicant, although evidence in humans is still limited with exposure linked to accelerated cognitive decline and an increased risk of Alzheimer's disease (AD) and related dementias. It acts as a neurotoxin that accumulates in the brain, promoting oxidative stress (OS), inflammation, and key AD pathologies like amyloid-β plaques. Chronic exposure is associated with higher AD mortality, particularly in those with genetic risks, such as the ApoE4, and in males. While evidence supporting the link between Cd exposure and AD is growing, some studies have noted that results can be sensitive to factors like study duration and biomarker types (blood vs. urine), requiring further research to fully understand the relationship.

This Article 2 is fully devoted to the study and effects of Cd on the human brain, especially its connection with AD, while following articles will deal with the other neurotoxic heavy metals.

Introduction

Neurotoxic heavy metals (NTHM) can lead to OS, inflammation, and disruption of the blood-brain barrier (BBB). These include: Aluminum (Al), which has been historically debated for its link to dementia (see Article 1 in this series); Arsenic (As) and Cd, which are environmental toxins that can accumulate in the brain, contributing to neurodegeneration; Lead (Pb), which is linked to impaired cognitive function and developmental issues in children; and Mercury (Hg), which is highly neurotoxic and is associated with memory loss and tremors (Table 1).

Metal	Neurological effect(s)	Notes
Aluminum (Al)	Link to dementia	Strongest evidence for extreme high-level exposures
Arsenic (As)	Contributes to neurodegeneration	Environmental toxin that can accumulate in the brain
Cadmium (Cd)	Contributes to neurodegeneration	Environmental toxin that can accumulate in the brain
Lead (Pb)	Linked to: o Impaired cognitive function o Developmental issues in children	Environmental toxin emitted from industrial plants and through lead pipes
Mercury (Hg)	Associated with memory loss and tremors	Highly neurotoxic

The basic physicochemical properties of Cd are summarized in Sidebar 1.

Table 1: Neurotoxic heavy metals and their neurological effects

Exposure levels

Among environmental factors, the roles of heavy metals such as Cd, Manganese (Mn), ad Pb are particularly of interest, given their widespread population exposure. Cd and Pb are notable metals for their neurotoxic effects even at the low levels of exposure encountered in the general population. On the other hand, Mn is an essential trace metal required for normal physiological functions including neuronal health but is toxic at low levels or in excess. Understanding the roles of these heavy metals in the etiology of AD and related dementias is critical and may lead to additional therapies.

Cd exposure is mostly measured in blood and urine biosamples. Blood-Cd levels represent current exposure (within approximately the last 75 days), while urine-Cd levels represent cumulative exposure (10–15 years) due to long-term retention in the kidneys. In the general population (≥1 year of age), the geometric mean blood level of Cd is 0.32 μg/L and the geometric mean urine level (≥6 years of age) is 0.19 μg/L. Cd levels are generally higher in women than men as low Iron (Fe) increases Cd absorption and are higher in smokers than non-smokers.

Cd enters the body via cigarette smoke, contaminated food (leafy vegetables, rice), and occupational exposure, with slow excretion allowing it to accumulate over a lifespan.

Major sources

Cd is naturally found in the Earth's crust. Anthropogenic sources include mining and refining, combustion of fossil fuels, waste incineration and disposal, and manufacture and application of phosphate fertilizers, making it environmentally persistent.

Diet is the primary exposure source and cigarette smoking is another important source for non-smokers and smokers alike. Ingestion of contaminated foods and inhalation of air Cd are major routes of exposure. While Cd is present in many common foods, consuming a varied diet and being mindful of high-risk items, particularly for sensitive groups like infants, helps manage intake.

While many foods contain trace amounts, the following are known for having particularly high concentrations: Grains (rice, wheat, barley, oats), cereal products, vegetables (leafy greens such as spinach, lettuce) and starchy roots (potatoes); nuts and legumes (peanuts, soybeans, sunflower seeds, beans, and lentils). Meats (organ meats such as liver and kidneys) and shellfish (seafood) often have higher levels. Other foods include dark chocolate (levels depend on cocoa solids), seaweed, and spices.

Cd levels vary because of soil uptake (plants absorb Cd from the soil, so contaminated soil leads to higher levels in crops like rice, potatoes, and tobacco, dietary patterns (vegetarians might have higher exposure due to greater intake of cereals, nuts, and pulses), and processing. Factors affecting Cd levels are the soil quality (levels are higher in crops grown near industrial areas, mining sites, or where phosphate fertilizers are heavily used); bioavailability (only about 1–10% of Cd in food is typically absorbed by the human body); and nutrition (a diet low in essential minerals like Fe, Ca, or Zn can increase how much Cd the body absorbs.

Other sources of exposure include smoking (tobacco leaves accumulate Cd, making smoking a significant source of exposure), water, and ceramics. In some areas, Cd can leach from metal pipes or certain ceramic ware into drinking water.

Production, uses, and releases to the environment

Production

Cd displays chemical similarity to Zinc (Zn), often occurring in Zn or lead (Pb) ore in relatively high concentrations. The Cd:Zn ratios in minerals and soils are within the range of 1:100 to 1:1000. Cd is obtained as a by-product of the refining of Zn and other metals, particularly copper (Cu) and Pb. There is no specific ore worth mining solely for its Cd content. The world consumption of the metal has increased continuously during the 20th century to a global supply of 22,000 metric tons as per the International Cadmium Association (ICA, 2002) and the supply has remained approximately at this level until the present. World refinery production was 25,000 metric tons in 2019 (U.S.) Geological Survey (USGS, 2020).

Although Cd toxicity has been recognized for only a century, environmental pollution has taken place for several thousand years, ever since humans started to produce metals from ores that happened to contain Cd.

Uses

Cd was used in several industrial processes but there are lower toxicity alternatives for most of its applications. In the 1970s, the Swedish Government introduced legislation to limit the use of Cd, and such legislation now is in effect in the European Union (E.U.), where Cd is classified as a *substance of very high concern with restricted uses.*

Because of its ability to protect Fe products from rusting, Cd was (and is still) used in some countries to coat steel through electroplating. For example, Cd stearate is used as a stabilizer in plastics. Because of its ability to stiffen Cu and increase its mechanical resistance at elevated temperatures, Cd is used in Cu-Cd alloys, which are used in items such as automobile radiators. Cd serves as an electrode component in alkaline batteries; this application is one of the most important current uses of Cd. It is also used in Silver (Ag) solders and welding electrodes. Cadmium telluride (CdTe) is increasingly used in solar panels. In the E.U., the use of Cd for plating is not allowed, and most applications of Cd compounds as pigments and stabilizers in plastics are banned. In the late 2010s, the global use of Cd was 79% for nickel-cadmium (NiCd) batteries, 11% for pigments, 7% for coatings, and 2% stabilizers (ICA, 2020).

Releases to the environment

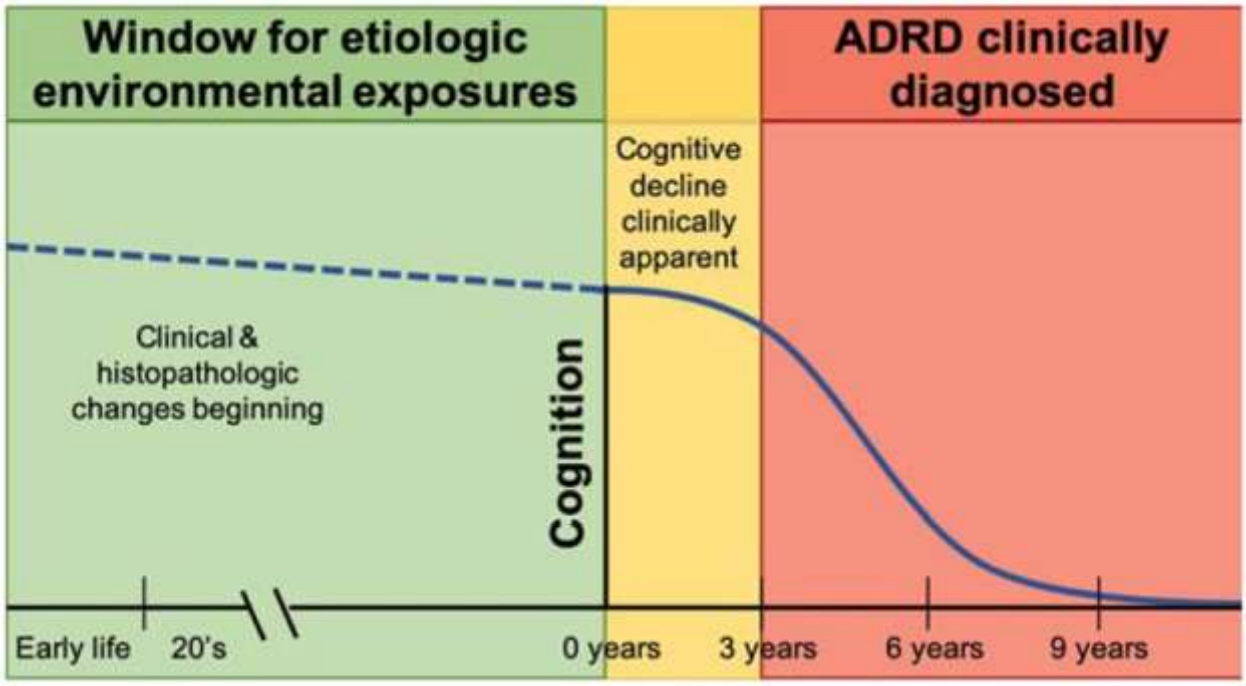
As an element, Cd occurs in the Earth's crust at levels of 8–100 µg/kg. It is released into the environment from natural and anthropogenic sources. The review by the United Nations Environment Program (UNEP, 2010) estimated the global emissions to air from natural sources to be ~150–88,000 tons/year (the wide range is explained by different estimates by scientists). Two different average estimates are as follows: Volcanoes: 820-1600 tons, sea salt spray: 60-2000 tons, natural fires: 110-13,000 tons, dust storms: 210-24,000 tons. Globally, weathering and erosion transports approximately 15,000 tons via rivers to the oceans. Oceans also receive Cd from the atmosphere by precipitation. In the oceans, Cd behaves as a nutrient-type metal and has a long residence time in sea water, estimated at 15,000 years.

As mentioned, the estimates of natural emissions of Cd to the atmosphere are uncertain. For anthropogenic sources, more precise information is available: Global emissions were 7,630 tons in 1980 and decreased to 2,850 tons in 2005. Of these emissions, 2,250 tons originated from the combustion of fossil fuels and waste. The remainder (610 tons) was from other industries, mainly from nonferrous metal production. Available data for inflow of Cd into the soil is limited

according to UNEP (2010). Data from the 1980s on global estimates report 5,600–7,400 tons/year, mainly estimated contribution of 4,300–7,400 tons from waste deposits.

Environmental effects

Identification of modifiable environmental risk factors can substantially impact prevention and treatment for AD and related dementias. Many environmental chemicals have long been known to be neurotoxic, particularly in laboratory models and in humans during neurodevelopment. In human populations, assessment of likely environmental factors during the risk window before disease manifestation is challenging due to the potentially long latency period of disease (Figure 2).



Source: Babulski et al. (2020)

Figure 2: Etiologic window for environmental exposures linked to Alzheimer's disease and related dementias

Transport to the brain and into neuronal cells

Absorption into the bloodstream and travel to the brain

Cd exposure from inhalation and ingestion sources interfaces with the gastrointestinal tract and the lungs, is taken up by these tissues, and enters the bloodstream. From precipitation from the atmosphere, but with an

The olfactory nervous system (ONS) may be a direct transport pathway of Cd to the brain and therefore, bypassing the BBB. Cd directly passes into the CNS through the ONS, causing persistent, irreversible damage by inhibiting adult neurogenesis in the hippocampus and olfactory bulb.

Under normal conditions, only small amounts of Cd can

cross the blood-brain barrier (BBB) in adults. The choroid plexus, a component of the blood-cerebrospinal access to the cerebrospinal fluid (CSF) and maintains internal central nervous system (CNS) homeostatic environment. Figure 3 illustrates the transport of Cd, Mn, and Pb to the brain.

Experimental evidence linking Cd and AD

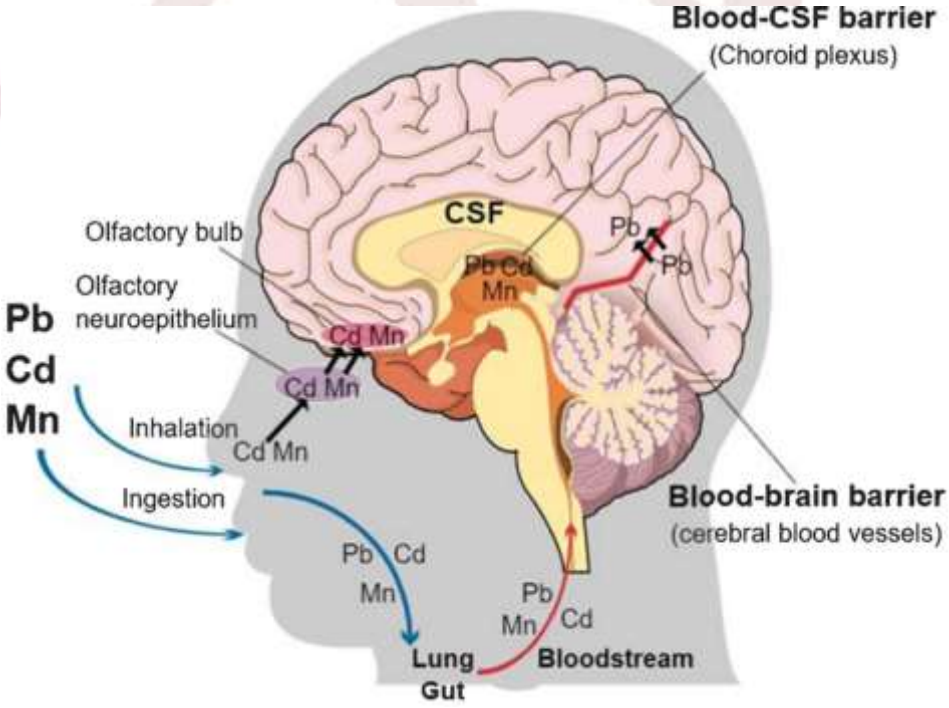
Genetic susceptibility

Research indicates that Cd exposure combined with the ApoE4 genotype (a major risk factor for Alzheimer's), significantly reduces neurogenesis (the production of new neurons) and worsens memory issues, especially in males.

Cd treatment and general neurotoxicity

Cd treatment induces oxidative stress (OS), fluid barrier (BCSFB), is the main site of Cd accumulation in the brain. It restricts blood toxicant neuroinflammation, and apoptosis in neuronal cells with well-defined direct effects. Toxicological studies support underlying biological mechanisms by which Cd exerts neurotoxic effects. Cd may also induce neurotoxicity by changing the permeability of the BBB and interacting with other neurotoxicants, leading to amyloid-beta (Aβ) aggregation and tau neurofibrillary tangle (NFT) production. Pathogenic processes following Cd exposure result in cognitive impairment and AD pathology.

Cd induces OS in neuronal cells and brain endothelial cells, initiating neurodegeneration signaling pathways. These signaling pathways are essential for the growth, proliferation, and survival of neurons; they are also central in synaptic plasticity and learning and memory formation in the brain.



Source: Babulski et al. (2020)

Figure 3: Transport of Cadmium, Lead, and Manganese to the brain

Metallothionein and trace metals also play a role in Cd neurotoxicity via signaling pathways. They are downregulated in the brain of AD patients and can protect against Cd toxicity by binding free Cd ions within cells. Insufficient production of Metallothionine by prolonged exposure to Cd causes neuronal apoptosis. Cd exposure disrupts intracellular Calcium (Ca) homeostasis and increases extracellular Ca influx, triggering neuronal apoptosis. Cd also impairs the cerebral microvascular endothelium and increases permeability of the BBB, disrupting brain ion balance and nutrient uptake.

Cd treatment and dysregulation of AD pathways

Animal studies support biological links between Cd exposure and Aβ aggregation and tau NFTs. Cd-treated mice showed deteriorated learning and memory abilities and senile plaque depositions in the brain. Cd treatment increases Aβ production and tau NFTs.

Cholinergic neuron toxicity is another potential Cd-AD pathway. Cd exposure increases cell death on cholinergic neurons, leading to alterations in acetylcholinesterase and degeneration of basal forebrain cholinergic neurons. Memory deficits seen in AD are associated with the loss of cholinergic neurotransmission due to degeneration of cholinergic neurons in the basal forebrain.

Neurotoxicity

Cd and the highly toxic compound Cadmium telluride (CdTe) can cross from the blood and accumulate in the brain, leading to significant neurotoxicity and accumulation in brain tissue by activating various signaling pathways involved in inflammation, OS and neuronal apoptosis. Exposure to Cd-based quantum dots (QDs) causes neuronal apoptosis, mitochondrial dysfunction, and cognitive deficits, with higher accumulation observed in females.

Cd poisoning has been reported from many parts of the world. It is one of the global health problems that affect many organs and, in some cases, can cause deaths annually. Long-term exposure to Cd through air, water, soil, and food leads to cancer and organ system toxicity such as skeletal, urinary, reproductive, cardiovascular, central and peripheral nervous, and respiratory systems. Cd levels can be measured in the blood, urine, hair, nail and saliva samples. Patients with Cd toxicity need gastrointestinal tract irrigation, supportive care, and chemical decontamination through traditional-based chelation therapy with appropriate new chelating agents and nanoparticle-based antidotes. Furthermore, it has been likewise recommended to determine the level of food contamination and suspicious areas, consider public education and awareness programs for the exposed people to prevent Cd poisoning.

The toxicity of CdTe itself is poorly characterized, but several studies have shown that it and its quantum dots (QD) are cytotoxic to mammalian cells. CdTe can cause severe pulmonary inflammation and fibrosis.

Mechanism of toxicity

Cd affects cell proliferation, differentiation, and apoptosis. These activities interact with DNA repair mechanism, the generation of reaction oxygen species (ROS) and the induction of apoptosis. Cd binds to the mitochondria and can inhibit both cellular respiration and oxidative phosphorylation at low concentration. Cd can induce ROS production and result in OS. This mechanism may express the role of Cd in organ toxicity, carcinogenicity and apoptotic cell death. It results in chromosomal aberrations, sister chromatid exchange, DNA strand breaks, and DNA- protein crosslinks in cell lines. Potentially, it may also cause mutations and chromosomal deletions.

Toxicity involves depletion of reduced glutathione, binds sulfhydryl groups with protein, and enhances production of ROS such as superoxide ion, hydrogen peroxide, and hydroxyl radicals. Cd also inhibits the activity of antioxidant enzymes, such as catalase, manganese-superoxide dismutase, and copper/zinc-dismutase.

Epidemiologic studies of Cd exposure and AD

Despite the dramatic worldwide production, consumption and release of Cd compounds in the environment show no efficient recycling way for them. Accordingly, human exposure to Cd compounds may create a serious health problem. An international collaborative study in 16 European countries has reported that the amount of Cd in mother-child couples exceeded the tolerable weekly intake. Nowadays, Cd exposure has decreased in many countries, but it has a very long biological half-life (10-30 years) and human activities related to Cd should be restricted to a minimal or no harmful level.

Postmortem brain Cd concentrations in AD

There are limited studies that examined the associations between Cd exposure and AD in human populations. A study using postmortem brain tissues found that AD brain tissues had higher concentrations of Cd (hippocampus: 0.547 g/g dry weight (d.w); cerebral cortex: 0.518 g/g d.w.) compared with age-matched control brain samples (hippocampus: 0.472 g/g d.w; cerebral cortex: 0.496 g/g d.w.) in an Eastern Canada sample but not in a United Kingdom sample.

In a recent study using postmortem brain samples from AD patients and non-demented elderly controls, Cd concentrations in the frontal cortex were lower in AD cases (20 ng/g) than in controls (30 ng/g). This finding should be interpreted with caution because AD patients (mean age = 78 years) were younger than non-demented controls (mean age = 88 years).

A meta-analysis including 8 studies covering 405 AD patients and 424 control subjects found that circulating concentrations (either whole blood, serum, or plasma) of Cd were significantly higher in AD (standardized mean difference = 0.62 (95% CI, 0.12, 1.11) versus controls. This same meta-analysis reported that circulating Pb concentrations were lower in AD patients. Again, it should be noted that the findings from postmortem brain tissues are subject to confounding by AD risk factors, especially age.

Exposure and cognitive decline, dementia and AD

Epidemiologic studies linking Cd exposure to AD risks (prevalence or incidence) have rarely been conducted due to methodologic challenges such as lack of relevant exposure data, low incident rate or prevalence, and late onset. Instead, a few studies have examined cognition as an early indicator of future AD risks, and they consistently report an association between Cd exposure and decreased cognitive function in older adults. A cross-sectional study with 2,068 older adults from the (U.S.) National Health and Nutrition Examination Survey (NHANES) 2011–2014 showed a significant association between Cd exposure measured in whole blood (median = 0.35 µg/L) and lower cognitive function. An earlier NHANES study reported an association between urinary-Cd, a longer-term biomarker of Cd exposure, and a measure of attention and perception only among never smokers, but not in the entire population.

Animal Studies

Experimental studies confirm that Cd exposure induces memory and cognitive deficits, mimicking Alzheimer's pathology in the brain.

Association with AD mortality

Studies, including analyses of NHANES data, have linked higher urinary Cd levels with an increased risk of death from AD.

Health effects of exposure to Cd

While CdTe has applications in biomedical imaging (as quantum dots) and high-resolution single photon emission computed tomography (SPECT) imaging, its toxicological profile highlights it as a serious environmental and occupational hazard to the CNS.

Cd crosses the BBB and damages neurons by inducing OS, suppressing antioxidant enzymes, and triggering inflammatory pathways. It accumulates in the brain and is linked to AD but also to amyotrophic lateral sclerosis (ALS), and Parkinson's disease (PD) – two other diseases not considered here. Long-term exposure results in memory impairment, anxiety, depression, and reduced locomotor activity.

The mechanism of action consists in the disruption of the balance of essential metals (like Ca and Zn) in neurons, affecting mitochondrial function and neurotransmission. The developmental damage results from exposure during critical brain development stages and can cause lifelong consequences, including impaired neurological maturation.

The health effects found in some individuals who have been exposed chronically to high levels of Cd include: Groups of workers, heavy smokers, people living in areas with high levels of environmental Cd and special exposure scenarios such as hobbies.

Sidebar 2 summarizes other observed health effects but are not of interest here.

Diagnostic evaluation

Cd levels in blood, urine, hair and nails samples are often determined in paraclinical laboratory tests.

Urine

Kidneys are the main organ to be affected by Cd in long term exposure. Urinary-Cd concentration equal to or greater than 0.5 µg/g creatinine is associated with renal damage. Also, the concentrations more than 2.0 µg/g of creatinine may be translated into extensive damage.

Tubular dysfunction followed by Cd nephrotoxicity increases urinary excretion of low molecular weight proteins. In this situation, sensitive tests (low molecular weight proteinuria) may be positive and mixed proteinuria (low and high molecular weight proteins excretion in urine) is seen.

Blood

The long Cd half-life (30 years) may be due to the long-term accumulation of Cd in the body but the short half-life of Cd in blood (three to four months) could be the result of a recent exposure. The limit of detection for blood-Cd concentration is 0.3 µg/L is measured by either electrothermal atomic- absorption spectrophotometry or the inductively coupled plasma mass spectrometry. The values at or below the limit of detection of Cd in all of participants are as follows: 1999-2000: 0.3µg/l; 2003-2004: 0.14µg/l; 2005-2010: 0.2µg/l.

Hair, nail, and saliva

Determination of the trace element levels in hair and nails is a subject of interest in biomedical sciences. Trace elements accumulate in the body in a long time, affecting biomedical and metabolic processes over time. Additionally, the sampling, transport and storage of hair and nails samples are easy and feasible and analysis of trace elements in the samples is cheap and fast.

Cd accumulates in the body for a long time, and its concentration can gradually increase several years after

exposure. Levels of Cd in the hairs have different reference values in various countries. Saliva analysis can be an excellent method for long term detection of heavy metal contamination. The mean level of Cd in saliva with tolerable standard limit in human body is less than 0.55 µg/l.

Application of nanomaterials

Nanomaterials have different applications such as tissue and organ engineering, medical instruments, drug delivery, diagnosis evaluation, prevention and management. Utilizing nanotechnology for diagnosing and eliminating toxic metals such as Cd can help to manage Cd intoxication and increase environment safety.

Several nanoparticles have been used for diagnostics. One of the nanoparticles is quantum dots (QDs). QDs are made of fluorescent labels of cadmium selenide (CdSe) or zinc sulfide (ZnS). When Cd poisoning occurs, it is released and enters cells containing zinc ions. Capping QDs with Zinc oxide (ZnO) effectively prevents Cd formation and achieves better material coverage. A gene expression test helps to determine this coating.

Treatment of Cd poisoning

Immediate considerations

After evaluation of the airways, breathing and circulation, protection and care is necessary. The gastrointestinal tract should be irrigated to remove Cd-containing solutions. Acute or chronic ingesting of Cd salts is rare, but it may lead to death. The lowest lethal dose of Cd is 5 gr in a 70 kg man. If emesis has not occurred, gastric lavage is performed soon. A small nasogastric tube must be used. Activated charcoal cannot effectively absorb the metal.

Hospitalization may help the patients exposed to Cd for evaluating the extent of liver damage, gastrointestinal, urinary and respiratory tracts followed by supportive therapy.

Natural and chemical decontamination

Industrial and mining activities may release Cd ions in wastewater. Natural decontamination can be introduced using some medicinal plants. The seeds of *Moringa oleifera*, *peanuts (Arachis hypogaea), cowpeas (Vigna unguiculata), urad (Vigna mungo) and corn (Zea mays)* were used for water purification. These seeds can absorb and neutralize colloidal positive charges. This action causes the absorption of the negative charged impurities and metals in wastewater.

Some plants are used for phytomediation to extract and detoxify some pollutants. They can accumulate heavy metals such as Cd, Chromium (Cr), Pb, Cobalt (Co), Ag, Se and Hg in their tissues. For example, Cleome Gynandra has been used as a phytoorigin detoxifier. Phytochelating activity has an important role in metal detoxification by the sequestration of Zn and Cd.

The removal of heavy metals from contaminated soil includes; 1) washing, leaching, flushing with chemical agents, 2) adding some non- toxic materials to reduce the solubility of heavy metals, 3) electromigration, 4) covering the original pollutants with clean materials, 5) mixing polluted materials with clean materials in surface and subsurface to reduce the concentration of heavy metals, and 6) phytoremediation by plants. The absorption yield depends on different factors such as the pH of environment, ionic power, and metal concentration in solution or biomass. These factors can affect biological storage, biogeochemical migration and toxic properties of heavy metals.

Chelating agents

• **Ethylenediaminetetraacetic acid (EDTA):** EDTA significantly increases urinary elimination of Cd.

However, it may increase Cd content in the kidneys and may increase the risk of renal dysfunction. Normal dose of EDTA is 500 mg of Ca2+ EDTA in combination with 50 mg/kg of glutathione (GSH) via IV infusion over the next 24 hours and repeated over 12 consecutive days. Renal dysfunction could be reversed if its initial urine-Cd concentration is <10 µg/gr of creatinine. Urine-Cd concentration more than 10 µg/gr of creatinine may induce irreversible renal damage.

• **Penicillamine (DPA):** Penicillamine, used previously to reduce toxic concentrations of Hg and Pb exposure, is not efficient in Cd overdose.

• **Dimercaprol:** Dimercaprol [British anti- Lewisite (BAL)] is an efficient antidote in heavy metal poisoning. BAL must be administered in the first 4 hours of poisoning. Deep intramuscular injection of a dose 3-4 mg/kg in gluteal muscle is recommended. It is given every 4 hours for the first two days, and twice daily for the next 10 days. It has been reported that Cd-BAL complex has more nephrotoxic effects than Cd alone, but the combination is not helpful. It is recommended to treat or manage actual poison exposure with other treatments. Possibly, BAL therapy may increase the risk of nephrotoxicity. In addition, it increases kidney and liver Cd burdens, may decrease survival, and enhances nephrotoxicity. For these reasons, it is not given in Cd intoxication.

• **Dithiocarbamates:** Dithiocarbamate derivatives have been used in many fields such as agriculture, manufacturing, and medicine. It may be useful for primary diagnostic evaluation of the efficacy of chelating agents. The efficacy has been confirmed in reducing Cd toxicity in animal studies. There is a necessity for the administration of these chelating agents in humans to be documented.

Combination therapy with chelating agents and other substances

Combination therapy is an effective route in the management of heavy metal toxicity. Optimal effects of chelating agent therapy may be achieved when combination of DMSA and MiADMSA is administered. A combination of DMSA and calcium trisodium diethylene triaminepentaacetate (CaDTPA) has been effectively used in acute oral Cd. These two agents reduce Cd concentration and toxic effect in the body. It has been found that N-acetyl cysteine (NAC) and DMPS reduced Cd–induced hepatic and renal metallothionein Also, NAC may increase the efficacy of DMPS.

Some reports have shown that antioxidants like vitamin C and vitamin E have protective effect against Cd-induced toxicity in different experimental animals. They can prevent or reduce many toxic effects of Cd on some organs and tissues such as the liver, kidney, skeleton, and blood. The other elements are Zn and Mn with many clinical applications. It has been suggested that Zn facilitates immune function and prevents free radicals. Mg is an essential cofactor to activate many enzyme systems in humans. Zn and Mg can reverse Cd-induced renal toxicity. Cd toxicity decreases antioxidant enzymes and produces ROS and lipid peroxidation. Chelating agents for Cd poisoning are ongoing, and may produce a new agent that is accessible, safe and effective, without aggravating end-organ. Nonetheless, overall, there is no evidence to justify the use of any chelator regarding the treatment of Cd toxicity.

Application of nanoparticles

Cd can be adsorbed by Aluminum oxide (Al2O3) nanoparticles. Generally, Al2O3 nanoparticles are appropriate for removing Zn and Cd from solution/sorbent systems. With low citrate concentrations, Al2O3 nanoparticles are used to remove Cd and Zn from contaminated solutions. Carbon nanotubes (CNTs) remove metal ions from aqueous solutions. Cd can be removed from wastewater by nanosized Titanium oxide (TiO2) particles.

Plasma exchange-hemodialysis-plasmapheresis

Plasma exchange may have started 24-36 hours after the appearance of clinical signs and symptoms, when life-threatening toxicity happened and the health team could not choose any alternative treatment. Plasma exchange must only be used in emergency situations. Hence, it can potentially be helpful in heavy-metal toxicity.

Hemoperfusion and hemodialysis are not useful in the treatment of Cd poisoning. Furthermore, Cd is eliminated very differently, it has very low residual renal function, and its dialysis is inefficient. In severe renal damage, hemodialysis has benefits in replacing kidney function. Some of the toxic substances can strongly bind to plasma proteins and cannot be removed through hemodialysis. Plasmapheresis is practical and sensible to remove protein-bound heavy metals in plasma. Nonetheless, there are no controlled studies on plasmapheresis in any specific intoxication.

The special case of Cadmium chloride

Cadmium chloride ($CdCl2$) is highly toxic and highly soluble in water. In addition to being primarily recognized as a known human carcinogen and a significant environmental hazard, it is also known for its cognitive and behavioral effects and is thus an AD factor of special interest.

Health and safety hazards

CdCl2 poses health and safety hazards in that it is extremely toxic with severe long-term risks, including:

• **Carcinogenicity:** Classified by the IARC and NTP as a Group 1 carcinogen, it is primarily linked to lung and prostate cancer.
• **Organ damage:** Chronic exposure leads to permanent kidney damage (proteinuria), bone diseases (osteoporosis, Itai-Itai disease), and reproductive harm.
• **Acute effects:** Inhaling fumes can cause pulmonary edema (fluid in the lungs) and "metal fume fever," a flu-like illness.
• **Environmental impact:** It is highly toxic to aquatic life with long-lasting effects.

Importantly, $CdCl2$ is a potent neurotoxicant that can cross the BBB and accumulate in the brain, particularly in the hippocampus and the cerebral cortex. Its primary effects involve triggering OS, disrupting neurotransmission, and promoting the development of neurodegenerative diseases, particularly AD.

Primary mechanisms of damage

The primary mechanisms of damage caused by $CdCl2$ are:

• **OS and inflammation:** $CdCl2$ induces the production of ROS and depletes antioxidants like Glutathione, leading to widespread cellular damage.
• **BBB disruption:** Chronic exposure increases the permeability of the BBB by damaging tight junction proteins (e.g., ZO-1), making it easier for more CD and other toxins to enter the brain.
• **Neurogenesis impairment:** It significantly reduces the production of new brain cells in the hippocampus, a region critical for learning and memory.
• **Mitochondrial dysfunction:** It interferes with the electron transport chain and opens the mitochondrial permeability transition pore, which halts energy production and triggers cell death (apoptosis).

Cognitive and behavioral effects

Cognitive and behavioral effects of CdCl2 are:

• **Memory impairment:** Exposure is linked to deficits in spatial and retention memory, and reduced learning ability.
• **Motor and sensory issues:** Occupational exposure has been associated with decreased psychomotor speed, altered equilibrium, and olfactory dysfunction (loss of smell).

• **Behavioral changes:** Studies have observed increased anxiety, aggressiveness, and sleep disturbances.

Link to neurodegenerative diseases

• **Alzheimer's disease:** C$dCl2$ promotes amyloid-beta (Aβ) aggregation and tau phosphorylation, hallmarks of AD. Individuals with the ApoE4 gene may be more vulnerable to these effects.
• **Parkinson's disease:** Evidence suggests CdCl2 may contribute to the death of motor neurons and is associated with Parkinsonism symptoms in some case reports.
• **Amyotrophic lateral sclerosis:** Higher blood and plasma levels of Cd have been noted in patients with motor neuron disease (MND) and sporadic amyotrophic lateral sclerosis (ALS).

Vulnerable populations

Vulnerable populations include:

• **Children:** They are more susceptible due to an immature BBB that allows higher Cd accumulation, potentially leading to learning disabilities and lower IQ.
• **Elderly:** Age-related breakdown of the BBB and the long biological half-life (up to 30 years) increase the risk for chronic neurotoxicity.

Therapies

While there is no medical "cure" for Cd poisoning, research has identified several protective strategies and nutritional antioxidants that may help mitigate its neurotoxic effects. These are:

• **Nutritional antioxidants and countermeasures:** Specific compounds have shown promise in laboratory studies for reducing $CdCl2$-induced OS in the brain.

• **Melatonin:** This hormone is a powerful antioxidant that can cross the BBB and has been shown to reduce lipid peroxidation and neuronal death caused by Cd.

• **Quercetin and curcumin:** These plant-based polyphenols may shield brain cells from inflammatory damage and help restore antioxidant enzyme levels.
• **Vitamins C and E:** When taken together, these vitamins can act as scavengers for free radicals generated by Cd, potentially slowing cognitive decline.
• **Essential minerals:** Adequate levels of Zn and Se are critical. Cd often "mimics" these minerals to enter cells. Maintaining healthy levels can competitively inhibit Cd uptake and support natural detoxification.

Preventative measures

Reducing exposure is the most effective way to protect brain health through the following measures:

• **Smoking cessation:** Tobacco plants readily absorb Cd from the soil, making cigarette smoke the primary source of exposure for the general population.
• **Dietary choices:** High levels of Cd can sometimes be found in organ meats (kidneys, liver), certain shellfish, and leafy greens grown in contaminated soil.
• **Occupational safety:** For those in battery manufacturing, welding, or pigments, strict adherence to HEPA-filtered respirators, protective clothing, and rigorous hand-washing is essential to prevent ingestion or inhalation.
• **Water filtration:** In areas near industrial sites or mines, using certified water filtration systems can reduce intake from drinking water.

Medical intervention

Medical intervention consists essentially in:

• **Chelation therapy:** In cases of acute poisoning, chelating agents (like Edetate calcium disodium, ECD) to bind the metal so it can be excreted. However, this must be performed under strict medical supervision as it can sometimes shift Cd to the kidneys.

Antioxidant research and dosages

While most studies are based on animal models or cell cultures, they offer insight into the potential protective dosages for the brain:

• **Zinc (Zn):** Supplements have been shown to reduce CD accumulation and alleviate OS in the brain. In rat studies, dosages of 30-60 mg/L in drinking water significantly protected brain enzyme activity.
• **Selenium (Se):** Acts as a cofactor for antioxidant enzymes like glutathione peroxidase, though its effectiveness may vary by neuronal subtype.
• **N-acetyl-L-cysteine (NAC):** Research indicates NAC can ameliorate memory impairment and prevent cell death in neuronal models by restoring glutathione pools.
• **Gallic acid:** In animal trials, 20 mg/kg body weight daily was found to abate CdCl2 toxicity by reducing oxidative markers.

Regulatory safety limits (2026)

The U.S. Government maintains strict limits to prevent chronic health issues like kidney damage and cancer:

Source	Category	Limit
OSHA	Workplace Air (8-hr TWA)	5 µg/m³
OSHA	Workplace Action Level	2.5 µg/m³
EPA	Drinking Water (MCL)	0.005 mg/L (5 ppb)
FDA	Bottled Water	0.005 mg/L
ATSDR	Chronic Oral Intake (MRL)	0.1 µg/kg/day

Table 3: Regulatory Cd safety limits

Medical monitoring triggers

Under OSHA's medical surveillance guidelines, specific biological levels trigger mandatory action:

• **Urinary Cd (Cd-U):** Action is required if levels exceed 3 µg/g creatinine.
• **Blood Cd (Cd-B):** Action is required if levels exceed 5 µg/L of whole blood.
• **Mandatory removal:** Employees must be removed from exposure if Cd-U exceeds 7 µg/g Cr or Cd-B exceeds 10 µg/L.

Safety protocols

Below are the safety protocols for handling the substance and a notable case study regarding exposure.

• **Laboratory and industrial handling protocols:** CdCl2 is strictly regulated. When working with it, people must follow these safety measures to prevent inhalation or skin contact.

• **Engineering controls:** Always use a certified chemical fume hood. Never handle the powder in open air, as the dust is easily inhaled.
• **Personal protective equipment (PPE):**
o **Gloves:** Nitrile or butyl rubber (double-gloving is recommended for high concentrations).
o **Respiratory:** A HEPA-filtered respirator (N100) if a fume hood is unavailable.
o **Body:** A dedicated lab coat and safety goggles/face shield.
• **Waste Disposal:** $CdCl2$ is a hazardous waste. It must be collected in a labeled, leak-proof container and disposed of through a licensed hazardous waste facility. Never pour it down the drain, as it is highly toxic to aquatic life.
• **Hygiene:** "Wash-out" protocols are vital. Employees should shower and change clothes before leaving the worksite to avoid bringing "take-home" Cd dust to their families.

Modern medical testing methods

Because Cd accumulates in different parts of the body over time, doctors use specific tests depending on the

type of exposure:

• **Urinary Cd test (Cd-U):** The "gold standard" for measuring chronic (long-term) exposure. It reflects the total body burden stored in the kidneys. Levels above 3 µg/g creatinine indicate significant exposure.
• **Blood Cd test (Cd-B):** Best for detecting recent or acute exposure (within the last few months). Since CD leaves the blood and moves into organs quickly, this test is less useful for historical exposure.
• **Beta-2 Microglobulin (β2M):** A urine test used to detect early kidney damage caused by Cd. If this protein is high, it suggests the kidneys are losing the ability to filter properly.
• **X-ray Fluorescence (XRF):** A specialized non-invasive tool that can measure Cd levels directly in the liver or bones, though this is typically used in research rather than standard clinics.

Conclusions and take-aways

- Cadmium is a toxic heavy metal released into the environment through both natural processes and human activities. The risk is significantly higher for the people with the ApoE4 gene.
- There is direct evidence for an interaction between this Alzheimer′s genetic risk gene and environmental exposures on accelerated cognitive impairment. However, the pathophysiologic link is limited given the uncertainty in Cadmium transport to the brain.
- Cadmium impairs the short-term spatial working memory in all animals. Overall, the interaction causes long-lasting and long-term changes in the brain.
- Cadmium compound poisoning leads to harmful effects on various organs and systems. It is considered as a potential worldwide threat to the environment and human beings.
- Long-term, chronic Cadmium exposure in humans can also lead to damage in various organs including the kidney, liver and bones.
- Several studies have indicated that Cadmium is also a neurotoxicant. It can cross from the blood and accumulate in the brain, causing neurotoxicity by activating various signaling pathways involved in inflammation, oxidative stress, and neuronal apoptosis.
- Cadmium levels in blood, urine, hair and nails samples as well as nanoparticles are often employed as diagnostic tests.
- Treatment of Cadmium poisoning includes natural and chemical decontamination, chelation through various agents, combination therapy with chelating agents and various other substances, application of nanoparticles, and plasma exchange-hemodialysis-plasmapheresis.
- The special case of Cadmium chloride was lastly considered. In addition to being primarily recognized as a known human carcinogen and a significant environmental hazard, it is also known for its cognitive and behavioral effects and is thus an AD factor of special interest.
- Sidebars will provide a primer on the basic physicochemical properties of Cadmium and other observed health effects of exposure to Cadmium.

Sidebar 1 – Physicochemical properties of Cadmium

Cadmium is a chemical element; it has symbol Cd and atomic number 48. This soft, silvery-white metal (see Figure 1) is chemically similar to the two other stable metals in group 12, Zinc Zn) and Mercury (Hg).

The average concentration of Cd in the Earth's crust is between 0.1 and 0.5 parts per million (ppm). It was discovered in 1817 simultaneously by Stromeyer and Hermann, both in Germany, as an impurity in Zn carbonate.

Cd occurs as a minor component in most Zn ores and is a byproduct of Zn production. It was used for a long time in the 1900s as a corrosion-resistant plating on steel, Cd compounds are used as red, orange, and yellow pigments, to color glass, and to stabilize plastic. Cd's use is generally decreasing because it is toxic. Because it is a neutron poison, Cd is also used as a component of control rods in nuclear fission reactors. One of its few new uses is in Cadmium telluride (CdTe) solar panels.

Cd has no known biological function in higher organisms.

Physical properties

Cd is a soft, malleable, ductile, silvery-white divalent metal. It is similar in many respects to Zn but forms complex compounds. Unlike most other metals, Cd is resistant to corrosion and is used as a protective plate on other metals. As a bulk metal, Cd is insoluble in water and is not flammable; however, in its powdered form it may burn and release toxic fumes.

Chemical properties

Cd burns in air to form brown amorphous cadmium oxide (CdO); the crystalline form of this compound is a dark red which changes color when heated, similar to Zinc oxide (ZnO). zinc oxide. Hydrochloric acid, sulfuric acid, and nitric acid dissolve Cd by forming cadmium chloride ($CdCl_2$), cadmium sulfate ($CdSO_4$), and cadmium nitrate ($Cd(NO_3)_2$), respectively.

Isotopes

Naturally occurring Cd is composed of eight isotopes. Two of them are radioactive, and three are expected to decay but have not measurably done so under laboratory conditions. Among the isotopes that do not occur naturally, the most long-lived are 109Cd with a half-life of 461.3 days, and 115Cd with a half-life of 53.46 hours. All the remaining radioactive isotopes have half-lives of less than 7 hours, and the majority have half-lives of less than 5 minutes. Cd has 8 known meta states, with the most stable being 113mCd ($t_{1/2}$ = 13.9 years), 115mCd ($t_{1/2}$ = 44.6 days), and 117mCd ($t_{1/2}$ = 3.44 hours).[16]

The known isotopes of cadmium range from 95Cd to 132Cd. For isotopes lighter than 112Cd, the primary decay mode is electron capture and the dominant decay product is element 47 (silver). Heavier isotopes decay mostly through beta emission producing element 49 (indium).

Sidebar 2 – Other observed health effects of exposure to Cadmium

Respiratory effects

The effects have been observed on the respiratory system. Most studies have associated chronic occupational exposure to Cd fumes and dusts with increased risk of chronic obstructive lung disease and emphysema, but some studies reported no such association. Study limitations, such as small sample size, lack of suitable cohorts, and failure to control for smoking and other confounding effects, render the association uncertain. There are also reports that respiratory effects caused by occupational exposure can reverse themselves if exposure stops.

There have also been studies examining the role of Cd in the development of chronic obstructive pulmonary disease (COPD) in smokers. The most recent study showed that current and former smokers had higher body burdens of Cd than non-smokers and that within smokers, the body burden of Cd was related to lung injury related to smoking. Cd might be important in the development of tobacco related lung disease. Further work needs to be done on this topic.

Chronic Cd inhalation is also suspected to be a possible cause of lung cancer. Other respiratory effects of chronic occupational exposure to Cd include chronic rhinitis, destruction of the olfactory epithelium with subsequent anosmia as well as the development of bronchitis.

Cardiovascular effects

In animals, chronic ingestion of Cd causes increased systolic blood pressure in the absence of significant renal disease. Such pressor effects have been linked to depressed blood and tissue levels of atrial natriuretic peptide, increased blood levels of aldosterone, and retention of sodium and water. This led to a hypothesis that Cd exposure in humans might be related to hypertension.

Recent studies have examined the contribution of Cd and some other heavy metals to the development of peripheral artery disease (PAD). These studies found an association with Cd exposure and the development of PD. In fact, the effect of smoking on PAD decreased after adjustment for Cd, suggesting that the effect of smoking on the development of PAD may be partially mediated by Cd.

Renal effects

The kidney is the principal organ targeted by chronic exposure to Cd. Cd nephrotoxicity may follow chronic inhalation or ingestion. Data from human studies suggest a latency period of approximately 10 years before clinical onset of renal damage, depending on intensity of exposure. However, subtle alterations of renal function have been described after acute exposure in animals, and there are rare reports of renal cortical necrosis after acute high-dose exposure in humans. Classically, chronic Cd exposure is associated with progressive renal tubular dysfunction.

Toxic effects on the kidney are dose related. For workers, the risk of clinical nephropathy increases significantly with total airborne exposures greater than 300 mg/m3, urine-Cd levels greater than 10 µg/g creatinine, and renal cortex levels greater than 200 ppm.

Early signs of renal damage have been reported in members of the general population at urine levels between 2-4 nmol/mmol creatinine. Several studies over the years have looked at the effects of Cd on the kidney in the environmentally exposed. These studies have found that even very low levels of Cd may have adverse effects on the kidney.

The World Health Organization (WHO) currently states that 200 µg/g levels wet weight in kidney causes adverse changes in 10% of the population. In the past, several studies of occupationally and environmentally exposed populations have shown that the threshold for renal damage occurred at urinary-Cd levels of 2-4 nmol/mmol creatinine.

Much work is underway to define the “critical renal concentration” at which Cd-induced renal damage occurs. There is a very low margin of safety between reaching the critical renal concentration and body burdens found in smokers. Recent work also suggests that exposed children might be a susceptible population.

At moderate, usual occupational levels of exposure, increased excretion of high-molecular-weight proteins, such as albumin and transferrin, are early signs of glomerular damage from Cd. Once begun, the

glomerular damage is believed to be irreversible, and the degree of damage is dose dependent. The glomerular filtration rate (GFR) declines slowly but progressively, suggesting that Cd accelerates the normal age-related decline in renal function. Clinical uremia is rare, but decreased filtration reserve capacity can be demonstrated in Cd workers with normal baseline GFR and serum creatinine. Cd exposure may also potentiate the development of glomerulopathy in diabetic populations.

Although Cd accumulates in bone, the bone disease that results from excessive Cd exposure is believed to be secondary to changes in Ca metabolism due to Cd-induced renal damage. Clinically significant bone lesions usually occur late in severe chronic Cd poisoning and include pseudo fractures and other effects of osteomalacia and osteoporosis. Pseudo fractures are spontaneous fractures that follow the distribution of stress in normal skeleton or occur at sites where major arteries cross the bone and cause mechanical stress through pulsation.

There is conflicting data that chronic cadmium exposure may cause mild anemia.

Other effects

Anosmia and yellowing of teeth have been reported.

Developmental effects

In animals, Cd crosses the placenta, and large parenteral doses during early gestation cause birth defects. During later pregnancy, doses greater than 2.5 mg/kg cause severe placental damage and fetal death.

Cd has not been reported to induce birth defects in infants of women occupationally exposed to Cd. Currently, the evidence of Cd's effects on pregnancy is inconsistent and requires further investigation.

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