Hindawi Publishing Corporation
The Scientific World Journal
Volume 2013, Article ID 394652, 7 pages
http://dx.doi.org/10.1155/2013/394652

Review Article

Cadmium Toxicity and Treatment

Robin A. Bernhoft

Bernhoft Centers for Advanced Medicine, 11677 San Vicente Blvd, Suite 208/211, Los Angeles, CA 93023, USA

Correspondence should be addressed to Robin A. Bernhoft; drb@drbernhoft.com

Received 15 January 2013; Accepted 28 February 2013

Academic Editors: H. Grant and D. K. Hansen

Cadmium is a heavy metal of considerable toxicity with destructive impact on most organ systems. It is widely distributed in humans, the chief sources of contamination being cigarette smoke, welding, and contaminated food and beverages. Toxic impacts are discussed and appear to be proportional to body burden of cadmium. Detoxification of cadmium with EDTA and other chelators is possible and has been shown to be therapeutically beneficial in humans and animals when done using established protocols.

1. Introduction

Cadmium (Cd) is a naturally occurring metal situated in the Periodic Table of the Elements between zinc (Zn) and mercury (Hg), with chemical behavior similar to Zn. It generally exists as a divalent cation, complexed with other elements (e.g., $CdCl_2$). Cd exists in the earth's crust at about 0.1 part per million [1], usually being found as an impurity in Zn or lead (Pb) deposits, and therefore being produced primarily as a byproduct of Zn or Pb smelting.

Commercially, Cd is used in television screens, lasers, batteries, paint pigments, cosmetics, and in galvanizing steel, as a barrier in nuclear fission, and was used with zinc to weld seals in lead water pipes prior to the 1960s. Approximately 600 metric tons are produced annually in the United States, and about 150 metric tons are imported [2].

Human exposure to Cd occurs chiefly through inhalation or ingestion. Ten to fifty percent of inhaled cadmium dust is absorbed, depending on particle size. Absorption through skin contact is negligible. About five to ten percent of ingested Cd is absorbed, also depending on particle size. Intestinal absorption is greater in persons with iron, calcium, or zinc deficiency [3].

Cigarette smoking is considered to be the most significant source of human cadmium exposure [4]. Blood and kidney Cd levels are consistently higher in smokers than nonsmokers. Inhalation due to industrial exposure can be significant in occupational settings. for example, welding or soldering, and can produce severe chemical pneumonitis [3].

Cadmium exposure occurs from ingestion of contaminated food (e.g., crustaceans, organ meats, leafy vegetables, rice from certain areas of Japan and China) or water (either from old Zn/Cd sealed water pipes or industrial pollution) and can produce long-term health effects. Contamination of drugs and dietary supplements may also be a source of contamination [5].

2. Absorption and Distribution

After absorption, Cd is transported throughout the body, usually bound to a sulfhydryl group-containing protein like metallothionein. About 30% deposits in the liver and 30% in the kidneys, with the rest distributed throughout the body, with a clearance half-life of twenty-five years [6]. The half life of cadmium in the blood has been estimated at 75 to 128 days, but this half life primarily represents deposition in organs, not clearance from the body [7]. Consequently, blood, hair, and urine Cd levels are poor surrogates for body burden and chiefly reflect recent exposure, as is also true with the other heavy metals. Accurate estimate of body burden of Cd will require urine provocation testing [8].

3. Mechanisms of Toxicity

Cadmium toxicity has been demonstrated in several organs, as discussed later. Cadmium induces tissue injury through creating oxidative stress [9–11], epigenetic changes in DNA

expression [12–14], inhibition or upregulation of transport pathways [15–17] particularly in the proximal S1 segment of the kidney tubule [18]. Other pathologic mechanisms include competitive interference with the physiologic action of Zn or Mg [19–21], inhibition of heme synthesis [22], and impairment of mitochondrial function potentially inducing apoptosis [23]. Depletion of glutathione has been observed, as has structural distortion of proteins due to Cd binding to sulfhydryl groups [24]. These effects are magnified by interaction with other toxic metals such as Pb and As [25] and possibly ameliorated by Zn or Se (see later) and by factors increasing levels of Nrf2 [26, 27].

4. Clinical Toxicity

Clinical stigmata of cadmium toxicity depend on route, quantity, and rate of exposure. The chief organ of toxic impact in the human is the kidney, where the S1 segment of the proximal tubule is a major target of Cd deposition, with clinically observable defects in protein, amino acid, glucose, bicarbonate, and phosphate reabsorption (Fanconi syndrome) resulting from Cd-induced oxidative damage to transport proteins and mitochondria which may induce apoptosis of tubular cells [28–31]. Effective antioxidant therapies are being sought [32], and there is *in vitro* evidence that selenium [33] and zinc [34] may at least partially antagonize the toxic effects of cadmium. About 30% of body cadmium is deposited in the kidney tubule region, as discussed earlier, with tubular damage being proportionate to the quantity of cadmium not bound to metallothionein [35]. Diabetics are more susceptible to renal tubular damage from Cd exposure than controls [36].

Cadmium may also impair Vitamin D metabolism in the kidney [37], with deleterious impact on bone. This effect, coupled with direct Cd impairment of gut absorption of calcium and derangement of collagen metabolism, can produce osteomalacia and/or osteoporosis [3]. The most extreme example of this process is *itai-itai* disease in Japan, which combines severe pain from osteomalacia with osteoporosis, renal tubular dysfunction, anemia, and calcium malabsorption [38].

Mechanisms of Cd toxicity in bone include stimulation of fibroblast growth factor 23 which induces phosphaturia and decreases phosphate uptake, leading to osteomalacia [39]. Cd is toxic to MC3T3 osteoblasts by unknown mechanisms [40] and stimulates osteoclasts, thereby inducing osteoporosis [41]. Cd decreases serum osteocalcin levels in rats [42]. These factors apparently combine to induce calciuria, increase bone resorption and decrease bone mineral density in Cd-exposed children [43].

Cadmium affects the cardiovascular system in several ways. The literature is somewhat contradictory, but much of it supports a role for Cd in inducing hypertension [44] and diabetes [45], with apparent direct toxic impact on gene transcription in the vascular endothelium [46]. Epidemiological evidence links Cd with sudden cardiac death [47], peripheral arterial disease [48], increased vascular intima media thickness [49], and myocardial infarction [50]. Proposed mechanisms include disruption of calcium channels and direct vasoconstriction as well as inhibition of NO and possibly other vasodilators [51]. Cd also directly induces oxidative stress, increases lipid peroxidation and depletes glutathione [52–54]. Cadmium accumulates in the wall of the aorta [55]. Cadmium is apparently brought into the vascular wall by Cd-laden monocytes which differentiate into foam cells [56]. Cadmium is also deposited in vascular smooth muscle cells and produces apoptosis of endothelial cells [57]. Direct myocardial structural damage has also been documented [58].

Hematopoeisis is adversely affected, most notably in *itai-itai* disease where severe anemia is observed, in association with marked suppression of erythropoietin production [59]. Hemolysis may also be a factor in producing Cd-associated anemia, which may produce iron-deficient indices despite increased body Fe stores resulting from hemolysis and increased duodenal Fe absorption [60].

Similarly, the immune system suffers form Cd-induced impairment at several levels. Prenatal Cd exposure may impair postnatal T cell production and response to immunization [61], as well as dysregulated thymocyte development [62]. Post-natal Cd exposures induce cell cycle arrest and apoptosis in splenocytes [63]. Cd induces increased rates of autoimmunity, increased production of nonspecific antibodies, and decreased production of antigen-specific antibodies [64]. Lymphocyte proliferation and natural killer cell activity are also suppressed by Cd [65]. Metallothionein protects against Cd immune toxicity [66].

Cadmium has considerable endocrine disruption capacity, apparently disregulating all pituitary hormones [67]. In the 2007-8 NHANES survey, elevated blood Cd levels were associated with suppressed TSH production, while increased urine Cd was associated with elevated serum levels of T3 and T4 [68].

Cadmium is considered to be a metalloestrogen, but evidence to support that contention is stronger in *in vitro* and *in vivo* animal studies than in population-based human studies [69]. It is based partly on binding of Cd to breast cancer estrogen receptors [70]. It seems that estrogen-like effects of Cd result from a mechanism different from that of steroidal estrogens [71].

Male infertility in rats from Cd exposure is due to damage to the blood-testis barrier, decreasing germ cell adhesion leading to germ cell loss, reduced sperm count and subfertility or infertility [72]. Rat studies further suggest Cd may induce production of prostaglandin F2alpha which causes cavernosal vasoconstriction and suppressed testosterone synthesis and secretion in the male, as well as destruction of corpus luteum and fetus in the female. These occur perhaps through inhibition of steroidogenic acute regulatory protein (StAR) which is responsible for the rate limiting step in steroidogenesis [73]. Human epidemiological studies have not, however, supported Cd as a cause of male infertility or erectile dysfunction.

Cadmium exposure is a known risk factor for developing insulin resistance [74, 75]. In the Korean NHANES experience, there is a strong correlation between blood Cd and development of metabolic syndrome [76], the mechanisms of which remain unelucidated but may involve mechanical distortion of the insulin receptor. The Cd effect on insulin resistance may be minimized by supplementation of Fe, Ca, Mg,

and Zn (which also decreases the Cd-associated risks of cancers, fractures, vascular disorders, and total mortality) [77].

Cadmium has been observed to cause oxidative stress and histologically visible membrane disturbances in the central nervous system, with reduction in acetylcholinesterase activity, increase in oxidative stress markers, depletion of glutathione, superoxide dismutase 2, and other antioxidants, and depletion of catalase, glutathione peroxidase, and glutathione-S-transferase [78]. These changes have apparently led to apoptosis of cortical cells in the central nervous system, possibly due to phosphorylation of calcium/calmodulin-dependent protein kinase II [79]. Cd can also inhibit influx through calcium channels [80].

Clinically, humans with elevated blood or urine Cd demonstrate decreased attention level and memory [81]. Additionally, humans with high urinary Cd levels had significantly decreased low-frequency hearing [82]. Similarly, rats with high urinary Cd exhibit decreased learning ability. Intranasal cadmium destroys olfactory nerve function in the rat [83]. Cadmium raises the frequency of spontaneous cortical electrical activity in the rat, lengthens the latency of sensory-evoked potentials, and impairs frequency following ability even in rats without detectable Cd brain deposition [84].

The United States Environmental Protection Agency considers Cd to be a Class B1 carcinogen [85]. There is contradictory evidence linking Cd exposure to breast cancer [86–88] and denying that link [89]. Prostate cancer is also correlated with Cd consumption [90, 91] as is pancreatic cancer [92–94]. In the Third NHANES cohort, Cd was associated with pancreatic and lung cancer and non-Hodgkin's lymphoma [95]. Other investigators have found a plausible association between Cd and lung cancer [96–98] and weak evidence for a link between Cd and non-Hodgkin's lymphoma [99, 100].

5. Reduction of Body Burden

There is no agreement in the literature regarding treatment of Cd toxicity. Human studies are few and anecdotal. While clinical protocols exist for the use of EDTA, DMPS, and DMSA [101–104], they rely for the most part on clinical experience and on *in vitro* and animal studies [105, 106]. EDTA is the agent most widely accepted for clinical use. While it may seem axiomatic that reduction of body Cd burden would decrease its toxic effects, not all authorities agree that active measures beyond avoidance are indicated, at least for acute poisoning, where concern exists that chelation may aggravate damage to the kidney tubules [107, 108]. For chronic exposures, however, there is considerable evidence of chelation's clinical efficacy, in humans and in experimental animals. Several chelators have been used. Clinically available chelators include EDTA, DMPS, DMSA, and British Anti-Lewisite (BAL). BAL is more toxic than its derivatives, DMPS and DMSA, and is seldom used clinically. Several experimental chelators, including DTPA [109] (available from the National Strategic Reserve for radiation poisoning), NaB [110], and others [111, 112], are also being investigated but are not clinically available at present.

It is clear that EDTA [113, 114], DMPS [115], and DMSA [116] increase urinary excretion of Cd, but DMSA seems to have little impact on overall body burden of Cd [117, 118]. Studies *in vitro* [119] and *in vivo* [120] suggest that EDTA is superior to DMSA in mobilizing intracellular Cd. In clinical use, EDTA is credited with an anecdotal report of relief of rheumatoid arthritis [121], as well as reduction of oxidative stress [122], and reduction of general metal toxicity [123, 124]. The efficacy of EDTA is apparently improved with concomitant use of glutathione [125] which also protects against nephrotoxicity; efficacy may also be improved with concomitant use of antioxidants [126] including mannitol [127], as well as thiamine [128], methionine [129], or zinc [130]. DMPS has not been studied as extensively as EDTA and DMSA but appears effective in rats [131], is available over the counter in Germany, and may be compounded legally in the United States.

EDTA is approved by the FDA for lead and other heavy metals, and has a long history of safe use. It should not be given faster than one gram per hour nor in dosage greater than three grams per session. Sessions should be at least five days apart, and replacement of essential minerals should be done orally between sessions. Several effective protocols exist implementing these principles [101–104].

Cd is also significantly present in sweat during sauna, which appears to be a moderately successful modality for reducing body burden of Cd without risk of tubular damage [132], albeit at a rate slower than that of intravenous chelation with EDTA.

6. Conclusion

According to the Third National Report on Human Exposure to Environmental Chemicals (NHANES), Cd exposure is widespread in the general population [133]. No standards exist correlating blood or urine Cd measurements with clinical toxicity; so, no conclusions are drawn on the significance of blood or urine levels. This is also true since blood and urine levels do not correlate with body burden, as discussed earlier. Given the ubiquity of Cd in the environment, the multisystem toxicity of Cd as discussed previous, and the generally benign nature of EDTA treatment administered under any of the aforementioed clinical protocols, it would seem reasonable to screen high risk individuals (smokers, persons with industrial exposures, etc., as above) and those with potential clinical indications and treat those with elevated Cd levels on provocation.

References

[1] K. Hans Wedepohl, "The composition of the continental crust," *Geochimica et Cosmochimica Acta*, vol. 59, no. 7, pp. 1217–1232, 1995.

[2] U. S. Geological Survey, *Mineral Commodity Summaries*, U.S. Geological Survey, Rolla, Mo, USA, 2012.

[3] G. F. Nordberg, K. Nogawa, M. Nordberg, and L. Friberg, "Cadmium," in *Chapter 23 in Handbook of the Toxicology of Metals*, G. F. Nordberg, B. F. Fowler, M. Nordberg, and L. Friberg, Eds., pp. 445–486, Elsevier, Amsterdam, The Netherlands, 3rd edition, 2007.

[4] L. Friberg, "Cadmium," *Annual Review of Public Health*, vol. 4, pp. 367–373, 1983.

[5] D. R. Abernethy, A. J. DeStefano, T. L. Cecil, K. Zaidi, and R. L. Williams, "Metal impurities in food and drugs," *Pharmaceutical Research*, vol. 27, no. 5, pp. 750–755, 2010.

[6] Argonne National Laboratories, *Cadmium, Human Health Fact Sheet*, Argonne National Laboratories, Lemont, Ill, USA, 2001.

[7] L. Jarup, A. Rogenfelt, and C. G. Elinder, "Biological half-time of cadmium in the blood of workers after cessation of exposure," *Scandinavian Journal of Work, Environment and Health*, vol. 9, no. 4, pp. 327–331, 1983.

[8] R. A. Bernhoft, "Mercury toxicity and treatment: a review of the literature," *Journal of Environmental and Public Health*, vol. 2012, Article ID 460508, 10 pages, 2012.

[9] V. Matović, A. Buha, Z. Bulat, and D. Dukić-Ćosić, "Cadmium toxicity revisited: focus on oxidative stress induction and interactions with zinc and magnesium," *Arhiv za Higijenu Rada i Toksikologiju*, vol. 62, no. 1, pp. 65–76, 2011.

[10] R. C. Patra, A. K. Rautray, and D. Swarup, "Oxidative stress in lead and cadmium toxicity and its amelioration," *Veterinary Medicine International*, vol. 2011, Article ID 457327, 2011.

[11] A. Cuypers, M. Plusquin, T. Remans et al., "Cadmium stress: an oxidative challenge," *BioMetals*, vol. 23, no. 5, pp. 927–940, 2010.

[12] B. Wang, C. Shao, Y. Li, Y. Tan, and L. Cai, "Cadmium and its epigenetic effects," *Current Medicinal Chemistry*, vol. 19, no. 16, pp. 2611–2620, 2012.

[13] R. Martinez-Zamudio and H. C. Ha, "Environmental epigenetics in metal exposure," *Epigenetics*, vol. 6, no. 7, pp. 820–827, 2011.

[14] C. Luparello, R. Sirchia, and A. Longo, "Cadmium as a transcriptional modulator in human cells," *Critical Reviews in Toxicology*, vol. 41, no. 1, pp. 75–82, 2011.

[15] F. Thévenod, "Catch me if you can! Novel aspects of cadmium transport in mammalian cells," *BioMetals*, vol. 23, no. 5, pp. 857–875, 2010.

[16] L. Wan and H. Zhang, "Cadmium toxicity: effects on cytoskeleton, vesicular trafficking and cell wall reconstruction," *Plant Signaling & Behavior*, vol. 7, no. 3, pp. 345–348, 2012.

[17] E. Van Kerkhove, V. Pennemans, and Q. Swennen, "Cadmium and transport of ions and substances across cell membranes and epithelia," *BioMetals*, vol. 23, no. 5, pp. 823–855, 2010.

[18] D. A. Vesey, "Transport pathways for cadmium in the intestine and kidney proximal tubule: focus on the interaction with essential metals," *Toxicology Letters*, vol. 198, no. 1, pp. 13–19, 2010.

[19] M. Abdulla and J. Chmielnicka, "New aspects on the distribution and metabolism of essential trace elements after dietary exposure to toxic metals," *Biological Trace Element Research*, vol. 23, pp. 25–53, 1989.

[20] J. M. Moulis, "Cellular mechanisms of cadmium toxicity related to the homeostasis of essential metals," *BioMetals*, vol. 23, no. 5, pp. 877–896, 2010.

[21] G. S. Shukla and R. L. Singhal, "The present status of biological effects of toxic metals in the environment: lead, cadmium, and manganese," *Canadian Journal of Physiology and Pharmacology*, vol. 62, no. 8, pp. 1015–1031, 1984.

[22] A. Schauder, A. Avital, and Z. Malik, "Regulation and gene expression of heme synthesis under heavy metal exposure—review," *Journal of Environmental Pathology, Toxicology and Oncology*, vol. 29, no. 2, pp. 137–158, 2010.

[23] G. Cannino, E. Ferruggia, C. Luparello, and A. M. Rinaldi, "Cadmium and mitochondria," *Mitochondrion*, vol. 9, no. 6, pp. 377–384, 2009.

[24] M. Valko, H. Morris, and M. T. D. Cronin, "Metals, toxicity and oxidative stress," *Current Medicinal Chemistry*, vol. 12, no. 10, pp. 1161–1208, 2005.

[25] M. H. Whittaker, G. Wang, X. Q. Chen et al., "Exposure to Pb, Cd and As mixtures potentiates the production of oxidative stress precursors," *Toxicology and Applied Pharmacology*, vol. 254, no. 2, pp. 154–166, 2011.

[26] L. Wang and E. P. Gallagher, "Role of Nrf2 antioxidant defense in mitigating cadmium-induced oxidative stress in the olfactory system of zebrafish," *Toxicology and Applied Pharmacology*, vol. 266, no. 2, pp. 177–186, 2012.

[27] K. C. Wu, J. J. Liu, and C. D. Klaassen, "Nrf2 activation prevents cadmium-induced acute liver injury," *Toxicology and Applied Pharmacology*, vol. 263, no. 1, pp. 14–20, 2012.

[28] F. Thévenod, "Nephrotoxicity and the proximal tubule: insights from Cadmium," *Nephron*, vol. 93, no. 4, pp. p87–p93, 2003.

[29] E. Sabath and M. L. Robles-Osorio, "Renal health and the environment: heavy metal nephrotoxicity," *Nefrologia*, vol. 32, no. 3, pp. 279–286, 2012.

[30] E. F. Madden and B. A. Fowler, "Mechanisms of nephrotoxicity from metal combinations: a review," *Drug and Chemical Toxicology*, vol. 23, no. 1, pp. 1–12, 2000.

[31] Y. Fujiwara, J. Y. Lee, M. Tokumoto et al., "Cadmium renal toxicity via apoptotic pathways," *Biological & Pharmaceutical Bulletin*, vol. 35, no. 11, pp. 1892–1897, 2012.

[32] G. Gobe and D. Crane, "Mitochondria, reactive oxygen species and cadmium toxicity in the kidney," *Toxicology Letters*, vol. 198, no. 1, pp. 49–55, 2010.

[33] I. Zwolak and H. Zaporowska, "Selenium interactions and toxicity: a review," *Cell Biology and Toxicology* , vol. 28, no. 1, pp. 31–46, 2012.

[34] A. R. Volpe, P. Cesare, P. Almola, M. Boscolo, G. Valle, and M. Carmignani, "Zinc opposes genotoxicity of cadmium and vanadium but not of lead," *Journal of Biological Regulators & Homeostatic Agents* , vol. 25, no. 4, pp. 589–601, 2011.

[35] M. Nordberg and G. F. Nordberg, "Chapter 8," in *Heavy Metals in the Environment*, B. Sarkar, Ed., pp. 231–270, Marcel Dekker, New York, NY, USA, 2002.

[36] A. Åkesson, T. Lundh, M. Vahter et al., "Tubular and glomerular kidney effects in Swedish women with low environmental cadmium exposure," *Environmental Health Perspectives*, vol. 113, no. 11, pp. 1627–1631, 2005.

[37] T. Kjellström, "Mechanism and epidemiology of bone effects of cadmium," *IARC Scientific Publications*, no. 118, pp. 301–310, 1992.

[38] T. Ogawa, E. Kobayashi, Y. Okubo, Y. Suwazono, T. Kido, and K. Nogawa, "Relationship among prevalence of patients with Itai-itai disease, prevalence of abnormal urinary findings, and cadmium concentrations in rice of individual hamlets in the Jinzu River basin, Toyama prefecture of Japan," *International Journal of Environmental Health Research*, vol. 14, no. 4, pp. 243–252, 2004.

[39] S. Kido, M. Fujihara, K. Nomura et al., "Fibroblast growth factor 23 mediates the phosphaturic effect of cadmium," *Nihon Eiselgaku Zasshi*, vol. 67, no. 4, pp. 464–471, 2012.

[40] J. Lizotte, E. Abed, C. Signo et al., "Expression of macrophage migration inhibitory factor by osteoblastic cells: protection against cadmium toxicity," *Toxicology Letters*, vol. 215, no. 3, pp. 167–173, 2012.

[41] X. Chen, G. Zhu, T. Jin et al., "Cadmium stimulates the osteoclastic differentiation of RAW264. 7 cells in presence of

osteoblasts," *Biological Trace Element Research*, vol. 146, no. 3, pp. 349–353, 2012.

[42] E. R. Youness, N. A. Mohammed, and F. A. Morsy, "Cadmium impact and osteoporosis: mechanism of action," *Toxicology Mechanisms and Methods*, vol. 22, no. 7, pp. 560–567, 2012.

[43] M. Sughis, J. Penders, V. Haufriod et al., "Bone resorption and environmental exposure to cadmium in children: a cross-sectional study," *Environmental Health*, vol. 10, p. 104, 2011.

[44] C. M. Gallagher and J. R. Meliker, "Blood and urine cadmium, blood pressure, and hypertension: a systematic review and meta-analysis," *Environmental Health Perspectives*, vol. 118, no. 12, pp. 1676–1684, 2010.

[45] J. R. Edwards and W. C. Prozialeck, "Cadmium, diabetes and chronic kidney disease," *Toxicology and Applied Pharmacology*, vol. 238, no. 3, pp. 289–293, 2009.

[46] D. Bernhard, A. Rossmann, B. Henderson, M. Kind, A. Seubert, and G. Wick, "Increased serum cadmium and strontium levels in young smokers: effects on arterial endothelial cell gene transcription," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 26, no. 4, pp. 833–838, 2006.

[47] A. Menke, P. Muntner, E. K. Silbergeld, E. A. Platz, and E. Guallar, "Cadmium levels in urine and mortality among U.S. adults," *Environmental Health Perspectives*, vol. 117, no. 2, pp. 190–196, 2009.

[48] A. Navas-Acien, E. K. Silbergeld, A. R. Sharrett, E. Calderon-Aranda, E. Selvin, and E. Guallar, "Metals in urine and peripheral arterial disease," *Environmental Health Perspectives*, vol. 113, no. 2, pp. 164–169, 2005.

[49] B. Messner, M. Knoflach, A. Seubert et al., "Cadmium is a novel and independent risk factor for early atherosclerosis mechanisms and in vivo relevance," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 29, no. 9, pp. 1392–1398, 2009.

[50] C. J. Everett and I. L. Frithsen, "Association of urinary cadmium and myocardial infarction," *Environmental Research*, vol. 106, no. 2, pp. 284–286, 2008.

[51] M. V. Varoni, D. Palomba, S. Gianorso, and V. Anania, "Cadmium as an environmental factor of hypertension in animals: new perspectives on mechanisms," *Veterinary Research Communications*, vol. 27, supplement 1, pp. 807–810, 2003.

[52] M. Valko, H. Morris, and M. T. D. Cronin, "Metals, toxicity and oxidative stress," *Current Medicinal Chemistry*, vol. 12, no. 10, pp. 1161–1208, 2005.

[53] H. Martynowicz, A. Skoczyńska, A. Wojakowska, and B. Turczyn, "Serum vasoactive agents in rats poisoned with cadmium," *International Journal of Occupational Medicine and Environmental Health*, vol. 17, no. 4, pp. 479–485, 2004.

[54] M. B. Wolf and J. W. Baynes, "Cadmium and mercury cause an oxidative stress-induced endothelial dysfunction," *BioMetals*, vol. 20, no. 1, pp. 73–81, 2007.

[55] S. Abu-Hayyeh, M. Sian, K. G. Jones, A. Manuel, and J. T. Powell, "Cadmium accumulation in aortas of smokers," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 21, no. 5, pp. 863–867, 2001.

[56] I. L. Steffensen, O. J. Mesna, E. Andruchow, E. Namork, K. Hylland, and R. A. Andersen, "Cytotoxicity and accumulation of Hg, Ag, Cd, Cu, Pb and Zn in human peripheral T and B lymphocytes and monocytes in vitro," *General Pharmacology*, vol. 25, no. 8, pp. 1621–1633, 1994.

[57] W. C. Prozialeck, J. R. Edwards, and J. M. Woods, "The vascular endothelium as a target of cadmium toxicity," *Life Sciences*, vol. 79, no. 16, pp. 1493–1506, 2006.

[58] M. L. Ferramola, M. F. Perez Diaz, S. M. Honore et al., "Cadmium-induced oxidative stress and histological damage in the myocardium," *Toxicology and Applied Pharmacology*, vol. 265, no. 3, pp. 380–389, 2012.

[59] H. Horiguchi, H. Teranishi, K. Niiya et al., "Hypoproduction of erythropoietin contributes to anemia in chronic cadmium intoxication: clinical study on Itai-itai disease in Japan," *Archives of Toxicology*, vol. 68, no. 10, pp. 632–636, 1994.

[60] H. Horiguchi, E. Oguma, and F. Kayama, "Cadmium induces anemia through interdependent progress of hemolysis, body iron accumulation, and insufficient erythropoietin production in rats," *Toxicological Sciences*, vol. 122, no. 1, pp. 198–210, 2011.

[61] M. L. Hanson, I. Holaskova, M. Elliott et al., "Prenatal cadmium exposure alters postnatal cell development and function," *Toxicology and Applied Pharmacology*, vol. 261, no. 2, pp. 196–203, 2012.

[62] M. L. Hanson, K. M. Brundage, R. Schafer, J. C. Tou, and J. B. Barnett, "Prenatal cadmium exposure dysregulates sonic hedgehog and Wnt/β-catenin signaling in the thymus resulting in altered thymocyte development," *Toxicology and Applied Pharmacology*, vol. 242, no. 2, pp. 136–145, 2010.

[63] S. Chatterjee, S. Kundu, S. Sengupta, and A. Bhattacharyya, "Divergence to apoptosis from ROS induced cell cycle arrest: effect of cadmium," *Mutation Research*, vol. 663, no. 1-2, pp. 22–31, 2009.

[64] M. Ohsawa, "Heavy metal-induced immunotoxicity and its mechanisms," *Yakugaku Zasshi*, vol. 129, no. 3, pp. 305–319, 2009.

[65] M. Fortier, F. Omara, J. Bernier, P. Brousseau, and M. Fournier, "Effects of physiological concentrations of heavy metals both individually and in mixtures on the viability and function of peripheral blood human leukocytes in vitro," *Journal of Toxicology and Environmental Health A*, vol. 71, no. 19, pp. 1327–1337, 2008.

[66] C. D. Klaassen, J. Liu, and B. A. Diwan, "Metallothionein protection of cadmium toxicity," *Toxicology and Applied Pharmacology*, vol. 238, no. 3, pp. 215–220, 2009.

[67] V. Jiménez-Ortega, P. Cano Barquilla, P. Fernández-Mateos et al., "Cadmium as an endocrine disruptor: correlation with anterior pituitary redox and circadian clock mechanisms and prevention by melatonin," *Free Radical Biology and Medicine*, vol. 53, no. 12, pp. 2287–2297, 2012.

[68] K. L. Yorita Christensen, "Metals in blood and urine, and thyroid function among adults in the United States 2007-2008," *International Journal of Hygiene and Environmental Health*, 2012.

[69] N. Silva, R. Peiris-John, R. Wickremasinghe et al., "Cadmium a metalloestrogen: are we convinced?" *Journal of Applied Toxicology*, vol. 35, no. 2, pp. 318–332, 2012.

[70] M. D. Johnson, N. Kenney, A. Stoica et al., "Cadmium mimics the in vivo effects of estrogen in the uterus and mammary gland," *Nature Medicine*, vol. 9, no. 8, pp. 1081–1084, 2003.

[71] I. Ali, P. Damdimopoulou, U. Stenius et al., "Cadmium-induced effects on cellular signaling pathways in the liver of transgenic estrogen reporter mice," *Toxicological Sciences*, vol. 127, no. 1, pp. 66–75, 2012.

[72] C. Y. Cheng and D. D. Mruk, "The blood-testis barrier and its implications for male contraception," *Pharmacological Reviews*, vol. 64, no. 1, pp. 16–64, 2012.

[73] D. Gunnarsson, M. Svensson, G. Selstam, and G. Nordberg, "Pronounced induction of testicular PGF2α and suppression of

testosterone by cadmium-prevention by zinc," *Toxicology*, vol. 200, no. 1, pp. 49–58, 2004.

[74] S. Satarug and M. R. Moore, "Emerging roles of cadmium and heme oxygenase in type-2 diabetes and cancer susceptibility," *The Tohoku Journal of Experimental Medicine*, vol. 228, no. 4, pp. 267–288, 2012.

[75] Y. W. Chen, C. Y. Yang, C. F. Huang, D. Z. Hung, Y. M. Leung, and S. H. Liu, "Heavy metals, islet function and diabetes development," *Islets*, vol. 1, no. 3, pp. 169–176, 2009.

[76] B. K. Lee and Y. Kim, "Blood cadmium, mercury, and lead and metabolic syndrome in South Korea: 2005–2010 Korean National Health and Nutrition Examination Survey," *American Journal of Industrial Medicine*, 2012.

[77] M. F. McCarty, "Zinc and multi-mineral supplementation should mitigate the pathogenic impact of cadmium exposure," *Medical Hypotheses*, vol. 79, no. 5, pp. 642–648, 2012.

[78] K. Shagirtha, M. Muthumani, and S. M. Prabu, "Melatonin abrogates cadmium induced oxidative stress related neurotoxicity in rats," *European Review for Medical and Pharmacological Sciences*, vol. 15, no. 9, pp. 1039–1050, 2011.

[79] S. Chen, Y. Xu, B. Xu, and M. Guo, "CaMKII is involved in cadmium activation of MAPK and mTOR pathways leading to neuronal cell death," *Journal of Neurochemistry*, vol. 119, no. 5, pp. 1108–1118, 2011.

[80] B. Bodereau-Dubois, O. List, D. Calas-List et al., "Transmembrane potential polarization, calcium influx, and receptor conformational state modulate the sensitivity of the imidacloprid-insensitive neuronal insect nicotinic acetylcholine receptor to neonicotinoid insecticides," *Journal of Pharmacology and Experimental Therapeutics*, vol. 341, no. 2, pp. 326–339, 2012.

[81] S. Pacini, M. G. Fiore, S. Magherini et al., "Could cadmium be responsible for some of the neurological signs and symptoms of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome," *Medical Hypotheses*, vol. 79, no. 3, pp. 403–407, 2012.

[82] J. Shargorodsky, S. G. Curhan, E. Henderson et al., "Heavy metals exposure and hearing loss in US adolescents," *Archives of Otolaryngology-Head and Neck Surgery*, vol. 137, no. 12, pp. 1183–1189, 2011.

[83] L. A. Czarnecki, A. H. Moberly, D. J. Turkel et al., "Functional rehabilitation of cadmium-induced neurotoxicity despite persistent peripheral pathophysiology in the olfactory system," *Toxicological Sciences*, vol. 126, no. 2, pp. 534–544, 2012.

[84] A. Papp, G. Oszlánczi, E. Horváth et al., "Consequences of subacute intratracheal exposure of rats to cadmium oxide nanoparticles: electrophysiological and toxicological effects," *Toxicology and Industrial Health*, vol. 28, no. 10, pp. 933–941, 2012.

[85] Cadmium Compounds, *Technology Transfer Network Air Toxics Web Site*, Environmental Protection Agency, Washington, DC, USA, 2007.

[86] N. B. Aquino, M. B. Sevigny, J. Sabangan et al., "The role of cadmium and nickel in estrogen receptor signaling and breast cancer: metalloestrogens or not," *Journal of Environmental Science and Health C*, vol. 30, no. 3, pp. 189–224, 2012.

[87] B. Julin, A. Wolk, L. Bergkvist, M. Bottai, and A. Akesson, "Dietary cadmium exposure and risk of postmenopausal breast cancer: a population-based prospective cohort study," *Cancer Research*, vol. 72, no. 6, pp. 1459–1466, 2012.

[88] H. Romanowicz-Makowska, E. Forma, M. Bryś et al., "Concentration of cadmium, nickel and aluminium in female breast cancer," *Polish Journal of Pathology*, vol. 62, no. 4, pp. 257–261, 2011.

[89] S. V. Adams, P. A. Newcomb, and E. White, "Dietary cadmium and risk of invasive postmenopausal breast cancer in the VITAL cohort," *Cancer Causes and Control*, vol. 23, no. 6, pp. 845–854, 2012.

[90] B. Julin, A. Wolk, J. E. Johansson et al., "Dietary cadmium exposure and prostate cancer incidence: a population-based prospective cohort study," *British Journal of Cancer*, vol. 107, no. 5, pp. 895–900, 2012.

[91] S. Guzel, L. Kiziler, B. Aydemir et al., "Association of Pb, Cd, and Se concentrations and oxidative damage-related markers in different grades of prostate csarcinoma," *Biological Trace Element Research*, pp. 1–10, 2011.

[92] R. Dobrila-Dintinjana, N. Vanis, M. Dintinjana et al., "Etiology and oncogenesis of pancreatic carcinoma," *Collegium Antropologicum*, vol. 36, no. 3, pp. 1063–1067, 2012.

[93] W. Qu, E. J. Tokar, A. J. Kim et al., "Chronic cadmium exposure in vitro causes acquisition of multiple tumor cell characteristics in human pancreatic epithelial cells," *Environmental Health Perspectives*, vol. 120, no. 9, pp. 1265–1271, 2012.

[94] A. F. Amaral, M. Porta, D. T. Silverman et al., "Pancreatic cancer risk and levels of trace elements," *Gut*, vol. 61, no. 11, pp. 1583–1588, 2012.

[95] S. V. Adams, M. N. Passarelli, and P. A. Newcomb, "Cadmium exposure and cancer mortality in the Third National Health and Nutrition Examination Survey cohort," *Occupational and Environmental Medicine*, vol. 69, no. 2, pp. 153–156, 2012.

[96] R. M. Park, L. T. Stayner, M. R. Petersen et al., "Cadmium and lung cancer mortality accounting for simultaneous arsenic exposure," *Occupational and Environmental Medicine*, vol. 69, no. 5, pp. 303–309, 2012.

[97] Y. S. Lin, J. L. Caffrey, J. W. Lin et al., "Increased risk of cancer mortality associated with cadmium exposures in older americans with low zinc intake," *Journal of Toxicology and Environmental Health A*, vol. 76, no. 1, pp. 1–15, 2013.

[98] F. Golbabaei, M. Seyedsomea, A. Ghahri et al., "Assessment of welders exposure to carcinogen metals from manual metal arc welding in gas transmission pipelines, iran," *Iranian Journal of Public Health*, vol. 41, no. 8, pp. 61–70, 2012.

[99] R. Ramis, P. Diggle, E. Boldo et al., "Analysis of matched geographical areas to study potential links between environmental exposure to oil refineries and non-Hodgkin lymphoma mortality in Spain," *International Journal of Health Geographics*, vol. 6, pp. 11–14, 2012.

[100] T. Kauppinen, E. Pukkala, A. Saalo, and A. J. Sasco, "Exposure to chemical carcinogens and risk of cancer among Finnish laboratory workers," *American Journal of Industrial Medicine*, vol. 44, no. 4, pp. 343–350, 2003.

[101] International College of Integrative Medicine, "Diagnostic and treatment protocols for safer, effective mercury human biohazard management," Tech. Rep., Consensus Development Working Group of the International College of Integrative Medicine, Bluffton, Ohio, USA, 2003.

[102] American College for Advancement in Medicine, *Chelation Module*, American College for Advancement in Medicine, Irvine, Calif, USA, 2010.

[103] Advanced Medical Education and Services Physician Associatio, *Introduction To Clinical Metal Toxicology*, Advanced Medical Education and Services Physician Association, San Antonio, Tex, USA, 2007.

[104] Autism Research Institute, *Clinician Seminar Level 1*, Autism Research Institute, San Diego, Calif, USA, 2010.

[105] C. Kelley, "Cadmium therapeutic agents," *Current Pharmaceutical Design*, vol. 5, no. 4, pp. 229–240, 1999.

[106] M. Blanuša, V. M. Varnai, M. Piasek, and K. Kostial, "Chelators as antidotes of metal toxicity: therapeutic and experimental aspects," *Current Medicinal Chemistry*, vol. 12, no. 23, pp. 2771–2794, 2005.

[107] G. F. Nordberg, K. Nogawa, M. Nordberg, and L. Friberg, "Cadmium," in *Chapter 23 in Handbook of the Toxicology of Metals*, G. F. Nordberg, B. F. Fowler, M. Nordberg, and L. Friberg, Eds., p. 479, Elsevier, Amsterdam, The Netherlands, 3rd edition, 2007.

[108] A. Gilman, F. S. Philips, R. P. Allen et al., "The treatment of acute cadmium intoxication in rabbits with 2, 3-dimercaptopropanol(BAL) and other mercaptans," *Journal of Pharmacology and Experimental Therapeutics*, vol. 87, supplement 4, pp. 85–101, 1946.

[109] O. Andersen, J. B. Nielsen, and P. Svendsen, "Oral cadmium chloride intoxication in mice: effects of chelation," *Toxicology*, vol. 52, no. 1-2, pp. 65–79, 1988.

[110] M. M. Jones, M. A. Basinger, R. J. Topping, G. R. Gale, S. G. Jones, and M. A. Holscher, "Meso-2,3-dimercaptosuccinic acid and sodium N-benzyl-N-dithiocarboxy-D-glucamine as antagonists for cadmium intoxication," *Archives of Toxicology*, vol. 62, no. 1, pp. 29–36, 1988.

[111] R. Ferreirós-Martínez, D. Esteban-Gómez, C. Platas-Iglesias, A. De Blas, and T. Rodríguez-Blas, "Selective chelation of Cd(II) and Pb(II) versus Ca(II) and Zn(II) by using octadentate ligands containing pyridinecarboxylate and pyridyl pendants," *Inorganic Chemistry*, vol. 48, no. 23, pp. 10976–10987, 2009.

[112] S. Gupta, J. R. Behari, S. Srivastava, M. Misra, and R. C. Srivastava, "Efficacy of liposome encapsulated triethylenetetraamine hexaacetic acid (TTHA) against cadmium intoxication: role of lipid composition," *Industrial Health*, vol. 33, no. 2, pp. 83–88, 1995.

[113] R. S. Waters, N. A. Bryden, K. Y. Patterson, C. Veillon, and R. A. Anderson, "EDTA chelation effects on urinary losses of cadmium, calcium, chromium, cobalt, copper, lead, magnesium, and zinc," *Biological Trace Element Research*, vol. 83, no. 3, pp. 207–221, 2001.

[114] C. Kelley, "Cadmium therapeutic agents," *Current Pharmaceutical Design*, vol. 5, no. 4, pp. 229–240, 1999.

[115] S. K. Tandon, S. Prasad, and S. Singh, "Chelation in metal intoxication: influence of cysteine or N-acetyl cysteine on the efficacy of 2,3-dimercaptopropane-1-sulphonate in the treatment of cadmium toxicity," *Journal of Applied Toxicology*, vol. 22, no. 1, pp. 67–71, 2002.

[116] C. D. Klaassen, M. P. Waalkes, and L. J. Cantilena Jr., "Alteration of tissue disposition of cadmium by chelating agents," *Environmental Health Perspectives*, vol. 54, pp. 233–242, 1983.

[117] G. R. Gale, L. M. Atkins, E. M. Walker Jr., and A. B. Smith, "Comparative effects of diethyldithiocarbamate, dimercaptosuccinate, and diethylenetriaminepentaacetate on organ distribution and excretion of cadmium," *Annals of Clinical and Laboratory Science*, vol. 13, no. 1, pp. 33–44, 1983.

[118] J. Nerudova, K. Blaha, A. Sokal, H. Jehlickova, and M. Cikrt, "Mobilization of aged cadmium from isolated rat hepatocytes by sulfhydryl chelators," *Polish Journal of Occupational Medicine and Environmental Health*, vol. 4, no. 4, pp. 349–358, 1991.

[119] E. Borenfreund and J. A. Puerner, "Cytotoxicity of metals, metal-metal and metal-chelator combinations assayed in vitro," *Toxicology*, vol. 39, no. 2, pp. 121–134, 1986.

[120] O. Andersen, J. B. Nielsen, and P. Svendsen, "Oral cadmium chloride intoxication in mice: effects of chelation," *Toxicology*, vol. 52, no. 1-2, pp. 65–79, 1988.

[121] F. Bamonti, A. Fulgenzi, C. Novembrino et al., "Metal chelation therapy in rheumathoid arthritis: a case report. Successful management of rheumathoid arthritis by metal chelation therapy," *Biometals*, vol. 24, no. 6, pp. 1093–1098, 2011.

[122] S. J. S. Flora, M. Mittal, and A. Mehta, "Heavy metal induced oxidative stress & its possible reversal by chelation therapy," *Indian Journal of Medical Research*, vol. 128, no. 4, pp. 501–523, 2008.

[123] M. Blanuša, V. M. Varnai, M. Piasek, and K. Kostial, "Chelators as antidotes of metal toxicity: therapeutic and experimental aspects," *Current Medicinal Chemistry*, vol. 12, no. 23, pp. 2771–2794, 2005.

[124] O. Andersen, "Chelation of cadmium," *Environmental Health Perspectives*, vol. 54, pp. 249–266, 1984.

[125] H. W. Gil, E. J. Kang, K. H. Lee, J. O. Yang, E. Y. Lee, and S. Y. Hong, "Effect of glutathione on the cadmium chelation of EDTA in a patient with cadmium intoxication," *Human and Experimental Toxicology*, vol. 30, no. 1, pp. 79–83, 2011.

[126] S. J. S. Flora, M. Mittal, and A. Mehta, "Heavy metal induced oxidative stress & its possible reversal by chelation therapy," *Indian Journal of Medical Research*, vol. 128, no. 4, pp. 501–523, 2008.

[127] S. K. Tandon, S. Singh, S. Prasad et al., "Reversal of cadmium induced oxidative stress by chelating agent, antioxidant or their combination in rat," *Toxicology Letters*, vol. 145, no. 3, pp. 211–217, 2003.

[128] S. K. Tandon and S. Prasad, "Effect of thiamine on the cadmium-chelating capacity of thiol compounds," *Human and Experimental Toxicology*, vol. 19, no. 9, pp. 523–528, 2000.

[129] S. K. Tandon, S. Singh, and S. Prasad, "Influence of methionine administration during chelation of cadmium by CaNa3DTPA and DMPS in the rat," *Environmental Toxicology and Pharmacology*, vol. 3, no. 3, pp. 159–165, 1997.

[130] S. J. Flora, U. Gubrelay, G. M. Kannan et al., "Effects of zinc supplementation during chelating agent administration in cadmium intoxication in rats," *Journal of Applied Toxicology*, vol. 18, no. 5, pp. 357–362, 1998.

[131] H. Vasken Aposhian, "Biological chelation: 2,3-dimercaptopropanesulfonic acid and meso-dimercaptosuccinic acid," *Advances in Enzyme Regulation C*, vol. 20, pp. 301–319, 1982.

[132] S. J. Genuis, D. Birkholz, I. Rodushkin et al., "Blood, urine, and sweat (BUS) study: monitoring and elimination of bioaccumulated toxic elements," *Archives of Environmental Contamination and Toxicology*, vol. 61, no. 2, pp. 344–357, 2010.

[133] Centers for Disease Control and Prevention, *Third National Report on Human Exposure To Environmental Chemicals*, Department of Health and Human Services, Atlanta, Ga, USA, 2005.