Title: **Cadmium: Carcinogen, Co-carcinogen and Anti-carcinogen**

Author: **Sandra M.Pinkham, M.D.**
Address: 2170 Riverside Drive, Columbus, OH 43221, 614-488-8256, FAX: 614-488-4736, e-mail:spinkham@iwaynet.net

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Introduction:

Cancer incidence and deaths continue to rise in Ohio (Figure 1) and around the world. In the last two decades there have been major changes in air pollution that could potentially affect many cancers. There has been a dramatic drop in lead (Pb) air pollution from the removal of Pb from gasoline combined with an increase in benzene, a carcinogen. Schroeder found that low level exposure to Pb resulted in female rats outliving male rats 4:1. They had a reduction in mammary tumors, neurologic disease, and liver and kidney disease compared to controls (Schroeder 1965). Pesticide and fertilizer use have risen sharply. All of these factors have increased the toxic effects of cadmium (Cd) air pollution. Cadmium is a ubiquitous pollutant present in tobacco smoke, incineration fumes, phosphate fertilizers and sewage sludge. With the increase in global population there is an increase in Cd air pollution.

In Japan the level of Cd in human kidneys has increased from 43.95 to 73.47 ug/g in the last decade in spite of a drop of Cd levels in food supplies (Noda 1993). Teenagers have levels approaching those of adults. A recent study (Elinder 1992) reported Cd levels of 5-160 ug/g in the kidneys of penguins living in Antarctica. Lichen studies done in Europe indicate that Cd is the only metal increasing in air (Sloof 1991). All these studies support the conclusion that Cd air pollution is an increasing global problem.

Of all the metals Cd is the most easily absorbed and the most influenced by nutritional factors. It has a special affinity for multiple sulfhydryl groups, but it binds weakly to so many other compounds that it moves to all compartments of the cell (Webb 1979). Very low Cd concentrations down to 100pM stimulate cell growth and DNA synthesis significantly (von Zglinicki 1992).

Cd increases free radicals, promotes lipid peroxidation, and depletes anti-oxidants (Ochi 1987, Pharikal 1988, Mukhopadhyay 1988, Morselt 1987). Cd affects ion transport through membranes (Kim 1988, Verbost 1987, Bevan 1989, Kopp 1986), energy availability through mitochondrial function (Toury 1985, Jamall 1987, Muller 1988), detoxification through microsomal enzymes (Alary 1989), intercellular communications by affecting cell adhesion in epithelial cells (Prozialeck 1991), and many cell signalling functions by affecting intracellular calcium (Verbost 1987), inositol polyphosphate, and protein kinase C (Smith 1989). Cd's behavior in complex mixtures is difficult to predict. It is influenced by many factors and it plays a pivotal role in stress responses. The stress response provides a first line of defense against infections and cancer transformation (Young 1989). Cd exposure, however, is associated with tumor formation and coupling of leukocytes, effects not generally found with other stressors in a model system of the skin of the common carp (Iger 1994). High dose Cd alone produced tumors in planaria, while PCB's and Aroclor 1254, a pesticide, did not initiate tumors but potentiated the tumorigenic effects of low dose Cd (Tehseen

1992, Schaeffer 1991).

Interactions:

Blakely (1987) found that Cd decreased the latency and increased the severity of a retroviral infection causing leukemia in mice. Cd activated Herpes simplex virus from a latent state in sensory neurons in mice (Fawl 1993). Other metals that induce metallothioneins did not have this effect. Continued administration of Cd increased the yield of infectious virus by 10 to 100 fold and prolonged the recovery of infectious virus from 6 to 11 days. Many cancers are associated with chronic viral infections. Zinc (Zn), nickel (Ni), or manganese (Mn) blocked the Cd-induced infectious virus.

Exposure to Cd increases over-growth by fungi. Aspergillus rhinitis developed in rats exposed to Cd but not those in the control group (Rehm 1988). In an area in Poland where human neoplasms and cattle leukemia were found, selenium (Se) deficiency was associated with the growth of this fungus (Dobrowolski 1993). With supplemental Se, a mineral that blocks Cd, the fungus and the cancers disappeared.

Zn and other ions, including Pb, can block Cd binding to the cell surface receptor which is associated with phospholipase C activation and inositol turnover (Smith 1989). A guanine nucleotide binding protein is involved. These proteins have a selenocysteine (Whanger 1987) which may be the binding site for these metals. This system is linked to calcium (Ca) mobilization and protein kinase C activation. These events play a role in such stress responses as platelet activation and aggregation and neutrophil activation.

Cd has complex interactions with metals, chemicals and hormones. Cd is antagonized by Zn and is synergistically toxic with copper (Cu), tin (Sn), and Ni (Geertz 1994). Antagonism and synergism were found with mercury (Hg) and Cd depending on concentration. Cd and Ni powders injected into different legs were far more potent in combination in inducing fibrosarcomas in female rats than males (Furst 1989). These 2 metals as sulfides stimulate H_2O_2 formation by human polymorphonuclear cells at 0.5 (Cd) and 1 nM (Ni) concentrations, comparable to effects of the tumor promotor 12-O-tetradecanoylphorbol-13-acetate. (Zhong 1990). The two metals have different effects. In a model system using murine sarcoma virus, Ni produced a splicing defect mutation while Cd and chromium (Cr) produced frameshift mutations (Chiocca 1989). Deletions of up to 300 nucleotides were noted with Cd exposure in this system (Heckman 1992). Cd, Cr, and Ni all inhibit DNA repair in mammalian cells and are co-mutagens with ultraviolet rays (Hartwig 1989).

Chemical carcinogens affect Cd and are affected by Cd exposure. Dioxins, pesticides, and herbicides bind to the estrogen receptor (Thornton 1993) and synergistic mixtures affect the estrogen receptor (Arnold 1996). Estrogen increases the uptake of Cd into the liver, kidneys, and mammary glands. It is possible that estrogenic substances can increase Cd uptake into mammary glands and other tissues with estrogen receptors. In a recent study of human breast cancer (Antila 1996), both normal and cancerous tissue had unexpectedly high levels of cadmium (3.2-86.9 in patients with cancer and 0.1-160-4 in healthy controls), equivalent to levels found in kidneys (Hahn 1987). Cigarette smoke exposure raised levels significantly. Moreover, both active and passive exposure to tobacco smoke appeared to increase the risk of breast cancer (Morabia 1996). Cd increases blood lipid levels which increases the

levels of fat soluble co-carciogens in the rest of the body (Leonzio 1992).

Gene Effects:

With exposure to Cd, organisms or cells increase their production of metallothionein (MT). Cd moves from the cell membrane to the nucleus where it binds to DNA, inducing gene transcription in as little as 4 hours (Fowler 1992). With chronic exposure gene duplications can occur (Maroni 1987). In Cd resistant cells the transcription of MT can increase 20-40 fold (Sequin 1987). In humans there are at least 14 genes that have been identified which control the production of MT (Gedamu 1987). A mutation that results in the loss of a charged amino acid at the hinge between the metal binding domains makes it ineffective (Cody 1993). Depending on a multitude of factors, free Cd, not Cd bound to metallothionein, produces toxicity both directly and indirectly through its many actions on phosphorylation of proteins and injurious effects on cell membranes and sensitive organelles (Sharma 1992, Webb 1979).

Starvation, infection, physical stress, inflammation, radiation, endotoxin, glucocorticoids, glucagon, catecholamines, calcium ionophores, estrogen, progesterone, interferons, interleukin-1, carbon tetrachloride, chloroform, ethanol, and alkylating agents are some of the stimuli that activate MT genes (Bremner 1987, Karin 1987). Interferon has been shown to protect cells from DNA damage caused by Cd (Vasil'eva 1989). Methylation of the MT gene affects gene expression (Bhave 1988). The promoters greatly modify the availability of free Cd.

Cd and Zn are physiologic antagonists. A Zn-dependent metal responsive element that induces MT-IIA gene does not respond to Cd at any dose (Otsuka 1993). Moreover, C-myc, which is induced by Cd (Jin 1990), represses Zn promoted isoforms of MT but not Cd or dexamethasone induced isoforms (Takeda 1994). Cd binds to a metal responsive element in the MT-1 promoter, activating it in Cd exposed and non-Cd exposed cells (Anderson 1990), suggesting that Cd plays a role in all stress responses, not just those caused by Cd exposure. Because it gets into cells readily, it can modulate any stress response.

If all goes well, Cd detoxifies itself. With Cd's ability to enter the cell through many channels and to affect many cell reactions that occur with stress responses, it is reasonable to consider Cd both a first and second messenger for the stress response that is highly conserved in nature. The induction of MT to bind free Cd is one of the ways to terminate the stress response so that the cell can return to normal housekeeping function.

Carcinogenesis:

Carcinogenic doses of Cd induce oxidative stress while impairing cellular defense mechanisms against such stress. With Cd-induced testicular cancer, 12 hours after exposure to Cd lipid peroxidation, iron (Fe) content, and cellular production of H_2O_2 were elevated in testicular Leydig cells (Koizumi 1992). It is evident that co-exposure to a variety of chemicals result in this carcinogenic state (Yamada 1993).

By altering cell metabolism, Cd fosters cell proliferation. In cell culture systems, this effect can be blocked by equimolar concentrations of Se (Webber 1985). The cell surface receptor activated by Cd (Smith 1989), interacts with oncogenes. Cd is known

to increase the expression of two oncogenes: c-myc and c-jun (Jin 1990). C-myc is associated with aggressive tumors. Cd also alters the tumor suppressor protein p53, eliminating its suppressant effect on cancers in a variety of tumors (Hainaut 1993).

In a situation of Zn deficiency, which always accompanies stress, there is inhibition of DNA repair, which is also significantly associated with carcinogenesis (Nocentini 1987). In any stress situation which results in a loss of tight epithelial junctions, either in the GI tract or in the vasculature, Cd is taken up by these lining cells and the transfer of nutrients is inhibited, compromising the cellular defenses.

Moreover, Cd effects on the primary tumor may allow shedding of tumor cells into the blood and the breaks in the vascular lining allow metastatic cells access to tissue. Cd has effects on proteases which are necessary for basement-membrane degradation and invasion of tumor cells.

Cathepsin D:

There have been several studies on the effects of Cd on cathepsin D, an important acid protease in lysosomes. Cd increases cathepsin D mRNA in human breast cancer cells (Garcia-Morales 1993). Over-expression of Cathepsin-D, by transfection increased metastases from rat tumor cells (1990). Cathepsin B increases mature cathepsin D in hormone refractory prostate tumor cells, promoting tumor invasion (Weiss 1993), an effect inhibited by a protease inhibitor. Elevated levels of cathepsin D were found in breast secretions from women with breast cancer (Sanchez 1993).

In human ovarian carcinoma cell lines, 1 nM 17-beta-estradiol increases secretion of procathepsin D by 50% (Rowlands 1993), an effect blocked by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). An inhibitory effect of TCDD on estrogen stimulated formation of lactate from glucose in human breast cancer cells was reversed by a phorbol ester, an effect that could involve Cd but that was not addressed in the study (Moore 1993). The increased incidence of reproductive tumors in fish and humans around pollution sources of Cd and dioxins suggests a synergistic effect.

Resistant Tumors:

Air pollution with Cd can make cancers resistant to cancer treatments. Tumors resistant to radiation and chemotherapy are resistant to Cd and may contain an overexpression of the MT gene. Overexpression of MT in primary invasive ductal carcinoma of the breast is associated with metastases which are resistant to anti-cancer drugs and radiation and have a poor prognosis (Schmidt 1993). Increased metallothionein concentration is found in human small cell lung cancer cells resistant to cisplatin and CdCl2 (Kasahara 1991). It is possible that the resistance blocks apoptosis.

Over-expression of heat shock protein 60 in ovarian cancer is associated with resistance to cis-platin therapy and a poor prognosis (Kimura 1993). In this study the researchers did not find an induction by Cd but they evaluated the cells at 4 hours. Hiranuma et al (1993) found that induction by Cd of this protein was maximal at 18 hours after exposure.

Over-expression of heme-oxygenase in human lung adenocarcinoma cell line (CL3R) is associated with resistance to Cd, arsenite, and adriamycin (Lee 1993). Heme-

oxygenase is induced by oxidant stress and Cd in conditions of low glutathione. Glutathione suppresses the induction of heme oxygenase (Sunderman 1987).

Anti-carcinogenesis:

Although Cd can be carcinogenic, especially in combination with other chemicals, it can induce apoptosis. Apoptosis is a gene regulated cell death associated with stress proteins (Lohmann 1993). Apoptosis is normal during embryogenesis and rids the body of stressed, infected, and cancerous cells (Wyllie 1987). Apoptosis occurs in cells with a fluid membrane which facilitates Cd uptake (Foulkes 1989), with increased intracellular calcium, an effect of Cd on the Ca ATPase (Verbost 1987), and a change in the expression of c-fos and c-myc (Lucas 1991), Cd effects (Jin 1990). Mammalian cells contain a Ca(2+)-dependent endonuclease which is a necessary step in apoptosis. Zn inhibits this process, depending on the free Ca2+ concentration. It appears that a balance between Zn and Ca regulates this process (Lohmann 1993). Cd alone stimulates the endonuclease, replacing Ca2+, and is more inhibitory than Zn in blocking apoptosis. This ability to take the place of both Zn and Ca and to have higher potencies than either ion, helps explain the highly divergent effects that it can produce.

As a stress agent Cd can both initiate and kill chemically or spontaneously initiated cancers of the lung, liver, and blood in rats (Waalkes 1991,1992). Lung tumors induced by certain chemical exposures in humans are inhibited in individuals who are heavy smokers. Unfortunately, smokers generally suffer from other toxic effects from Cd exposure.

Female Cancers:

With the reduction in atmospheric Pb, which antagonizes the effects of Cd, and the increase in environmental chemicals that bind to the estrogen receptor combined with Cd pollution, one can predict a change in female morbidity and mortality. The increase in breast cancer could be in response to Cd. Infiltrating inflammatory cells in the stroma appear to be the source of cathespin D levels associated with enhanced metastatic potential of node negative cancers (Johnson 1993), an effect that Cd could promote. Cd induces human mononuclear cells to produce large amounts of interleukin-8, which is the cytokine causing neutrophil infiltration (Horiguchi 1993). Cathepsin D stimulates the release of transforming growth factor-alpha (TGF-alpha), which stimulates breast cell growth by binding to TGF-alpha/epidermal growth factor receptors on the cell surface (Henry 1992). Metastases from human breast tumor cells grown in mice without estrogen supplementation, are associated with elevated cell production of cathepsin D (Thompson 1993).

The behavior of dioxins is particularly problematic. 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) acts as liver tumor promoter in female rats but not male rats (Schrenk 1992). In the human breast cancer cell line MCF-7, TCDD acts as an anti-estrogen but when combined with a phorbol ester the anti-estrogen response is inhibited (Moore 1993). In areas in Maine and Florida contaminated with herbicides there are increased reproductive tumors in clams and increased human mortality rates due to ovarian cancer (Brown 1993). The herbicides are contaminated with TCDD and air pollution with Cd would act as a co-carcinogen. Tamoxifen, an anti-estrogen commonly used in

breast cancer therapy, although non-toxic when administered alone, in conjunction with administration of TCDD caused a centrilobular pattern of hepatocellular degeneration and necrosis with perivascular infiltration of inflammatory cells in female CD1 mice ((MacKenzie 1992). A co-toxic effect with ambient Cd pollution could explain this dramatic effect on toxicity. A protective effect by lipoic acid, which blocks Cd-induced hepato-toxicity (Muller 1989) would support the hypothesis of Cd involvement.

Such complex interactions are also seen with dehydroepiandrosterone(DHEA) which inhibits growth of mammary cancer cells in intact rats but stimulates it in ovariectomized, estrogen deficient animals. This has led to the hypothesis that low DHEA increases mammary carcinoma risk in premenopausal women (Ebeling 1994). Cd is taken up more readily by the female adrenal than the male. It has inhibitory effects on basal and ACTH-stimulated steroidogenesis (Mgbonyebu 1993). With stress and pollution producing lower levels of DHEA, increased breast cancer could result in premenopausal women and those receiving hormone replacement therapy.

Chronic cervicitis and cervical cancer are increased in smokers (Bartecchi 1994) and associated with human papilloma virus. It is likely that Cd facilitates the carcinogenic effects of the virus which it does with murine retrovirus infections.

Male Tumors:

Prostate cancer has been associated with increased Cd levels in the soil in Spain (Garcia Sanchez 1992). It is one of the cancers that has been increasing in incidence and severity. Older patients in Utah with aggressive tumors had a higher intake of dietary fat (West 1991), a source of added pesticides. Cd exposure from occupational exposure, high dietary intake, or smoking increased the risk for aggressive prostate tumors (Elghany 1990). Men employed as janitors had greatly increased risk for aggressive tumors in this study. The carcinogen 3,2'-dimethyl-4-aminobiphenyl when combined with Cd produced significantly more prostate carcinomas in rats than either chemical given alone, showing a synergistic effect (Shirai 1993). Janitors are exposed to Cd in dust and other toxic chemicals in cleaning supplies.

Experimentally Cd can produce testicular and prostate cancers in rodents (Koizumi 1992, Waalkes 1991,1992).

Lung, Bladder and Colon Cancer:

Synergy of Cd with other carcinogenic chemicals undoubtedly plays a role in the development of lung cancer in smokers and non-smokers exposed to passive smoke. The effects of such synergy have been studied in rats using Cd, n-nitrosoheptamethyleneimine, (NHMI) and asbestos fibers to produce lung cancer (Harrison 1986, 1988). In one study using chrysolite asbestos, added Cd had no additional effect which led the authors to conclude that Cd had no influence. An alternative explanation is that the ambient level in the tissue made the added chemicals carcinogenic and the addition of more Cd had no added effect. In a previous study by the same scientists the lung tumor incidence was highest in the group of animals receiving crocidolite, another kind of asbestos particle, Cd and NHMI (Harrison 1986). Elevated levels of Cd, Ni and Cr are found in lung cancer and colorectal cancer and the

metal levels are correlated with blood levels of tumor markers (Martin Mateo 1990).

Workers exposed to 4-aminobiphenyl, which is a potent bladder carcinogen, who developed chloracne from exposure to dioxin (TCDD) in 1949, had increased mortality from soft tissue sarcoma, bladder cancer and respiratory cancer (Collins 1993). Since 4-aminobiphenyl is a co-carcinogen with Cd it is likely that Cd could be a co-carcinogen with dioxin and 4-aminobiphenyl.

Clinical Evaluation of Cd Exposure and Toxicity:

1. In most instances, one can find evidences for Cd exposure from environmental sources and active and passive smoke exposure. Urinary-cotinine is correlated with blood Cd (Willers 1992). Co-exposure to physical, emotional, chemical, or biological stressors, nutritional deficiencies, exaggerated responses to stress with psycho-neuro-endo-immune alterations, and genetic susceptibility are factors that suggest increased levels of free Cd. There is a wide variability in sensitivity to the toxicity of Cd ions (Sens 1994).

2. Free Cd is not measured by blood, urine and hair Cd levels. Mag-fura-2 can be used to measure free Cd levels in cells (Quamme 1992). The Cd concentration in blood collected at autopsy is several hundred times higher than values measured before death. Formalin fixative greatly reduces the level of Cd found in tissues (Koizumi 1994).

3. By exposing dispersed cancer cells to varying concentrations of Cd and evaluating their viability in 24 hours, it should be possible to identify Cd sensitivity or resistance before the administration of radiation or chemotherapy, which might aggravate the condition of patients with resistant tumors. Cd effects on gene expression, such as over-expression of the MT gene, heat shock protein 60, or heme oxygenase can be used to identify Cd resistance in cancer cells using immunological stains.

4. Decreased anti-oxidants, lipid peroxidation, elevation of LDH, Alk Phosphatase, eosinophilia, lymphopenia, elevated monocytes, fever, cachexia, viral, bacterial and fungal infection, neurotoxicity, fatigue, and muscle weakness are non-specific effects of increased free Cd.

Therapeutics:

1. Cd could be used therapeutically in cancer treatments to induce apoptosis in Cd sensitive tumor cells. Anti-sense oligonucleotides complimentary to the messenger RNA coding for MT-II increased the sensitivity of neuroblastoma cells to Cd (Iversen 1992).

2. Anti-fungal herbs have anti-carcinogenic effects and chelate and remove Cd, ie Garlic, Pau D'Arco, and licorice.

3. High doses of vitamin C eliminate plasmids in bacteria which confer cadmium resistance. It is conceivable that high doses of vitamin C could make cancer cells Cd

sensitive as well.

4. Cd can be used therapeutically in gene therapy to incorporate plasmids and promote gene expression. These attributes could be used in new gene therapies to restore the very malfunctions it may have caused.

5. Mg and Zn protect normal cells from toxic effects of chemotherapeutic agents which may occur in conjunction with released Cd. Niacin as NAD, protects DNA from oxidative strand breaks (Zhang 1993), so a deficiency would have a cancer promoting effect. Zn deficiency prevents the mobilization of vitamin A, another cancer fighting vitamin from the liver.

6. N-acetyl-cysteine facilitates Cd excretion, increases intracellular glutathione, and prevents the production of interleukin-8 induced by Cd, as does EDTA, a metal chelator (Horiguchi 1993).

Summary:

As a stress agent, inducing apoptosis and blocking it, Cd can have both helpful and harmful effects. The atmosphere is a thin envelope which makes the world a global village. Cd is the most toxic metal in air. As both the first and second messenger of the stress response, it is synergistically toxic with all other stressors, including many other carcinogens. Elimination of Pb and its replacement with added benzene in gasoline appears to have increased the toxicity of atmospheric Cd. With scientific understanding of the molecular basis of Cd's role in carcinogenesis and anti-carcinogenesis, primary cancer prevention can be practiced by reducing Cd and chemical air pollution and educating the public on smoke cessation, healthy eating habits and stress reduction. Using the existing information on Cd and its effects, determinations could be made on established cancers so that individualized treatment protocols can be developed to improve patient care.

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Figure 1