ASSESSMENT OF CADMIUM AIR POLLUTION EFFECTS. Sandra M. Stewart-Pinkham, Columbus, OH 43

Introduction:

Change is constant in nature. Nevertheless, the rapid increase in human population, accompanied by rising infections, cancers, societal violence, global species loss, and global weather changes are compelling reasons to look carefully at those global environmental factors that might be influencing these changes in order to see if they might be amenable to some kind of control. Evaluating and analyzing global processes require a new kind of problem solving that can deal with inherent unresolvable uncertainties and complexities.

In the past, global problems have been difficult to study scientifically because they can't be solved with classical methods of scientific proof due to non-linear effects, inter-dependent variables, and confounding factors. Because of the critical importance of our global problems, we can no longer afford to ignore what we cannot thoroughly know (Funtowicz 1994). Assessing the effects of global cadmium (Cd) air pollution is an example of this new kind of problem solving.

The task of assessing the effects of Cd air pollution is daunting. There are irregular releases of Cd into air coming from such natural sources as volcanoes and forest fires (Mislin 1987). A relentless increase in Cd air pollution accompanies population growth because Cd air pollution comes from coal and oil combustion, non-iron metal production, steel and iron manufacture, refuse incineration (municipal and sewage sludge), phosphate fertilizers, cement production, and wood production (Garty 1993).

Natural and human sources affect plants, whose rapid growth causes a changing cycle of metabolic uptake of Cd from the environment and whose cell death releases Cd back into the environment. When snow melts in the spring, Cd is suddenly released (Abrahams 1988), contributing to springtime increases in Cd in food, air pollution, and animal tissues. High temperatures and wind conditions increase release of Cd from plants into air (Beauford 1977).

In this century lead (Pb) pollution from the combustion of leaded gasoline rose until 1970 and subsequently fell back to its 1900 level. It is significant that Pb can block Cd uptake into plants, blocking its passage back into air (Djingova 1933). Hence, the recent global decrease in Pb levels is allowing Cd levels to climb even higher.

The production, use and pollution by a great variety of chemicals in agriculture and industry has affected global air. In particular, the incineration of biologicals has increased release of hydrogen chloride, which reacts readily with Cd compounds to produce Cd chloride, a highly

inflammatory compound (Oberdoerster 1992) due to its high solubility. As the relative ratio of Pb and Cd has changed dramatically over this century, the form of Cd has also changed to a more soluble compound, and the consequent bioexposure has been to Cd in interaction with other organics and metals.

Although Cd is a highly toxic metal (Gordon 1990, Lag 1987), Cd air pollution is not generally recognized to be a major environmental and health issue. Using conventional scientific approaches, it has been difficult to find agreement on the extent of Cd exposure, the role of air pollution as a route of exposure, and effects solely attributable to Cd. Scientists, have felt there was insufficient proof to implicate Cd in any one of these problems under discussion.

Fox (1991) suggests that it is better to accept as true what cannot be perfectly proved, even though it might be wrong, if doing so can lead to actions to protect the ecosystem. He calls this the precautionary principle.

Using his guidelines, assessments of Cd exposure and toxicity in this paper will be based on data from a wide variety of sources: algae, lichens, mice, beavers, trees, and humans, since all cells are affected by it. Because of its unique ability to interact with other minerals, chemicals, and biological agents, these effects will be presented. New information on its effects from a molecular perspective will be explored. Health effects exhibited in one species will raise the possibility that the same or related health effects are occurring

in other species, including humans. Multiple health effects, rather than specific diseases in isolation, will be considered. Finally, implications for public policy will be examined.

Exposure:

One of the first problems in assessing Cd air pollution is to determine the extent of exposure. Quartz filters which are used to collect Cd samples in air no longer trap Cd efficiently. Particulates, which used to adsorb atmospheric Cd so that it could be measured in standard air filters, have fallen dramatically with the decline in use of leaded gasoline.

The use of plants and animals as monitors is necessary with a bioavailable metal like Cd, but it can be confusing. Although plants and animals actively absorb Cd, they either accumulate it or exclude it. Species with high and low levels of Cd can exist in the same locale and these levels can change with the seasons and other influences.

Wind and high temperature move Cd from plants back into the atmosphere (Beauford 1977). From water surfaces and fields, Cd can be released back into air keeping soil and water levels relatively low in spite of high levels of air pollution. Wetlands are a complex system which can trap Cd but also release it back into the atmosphere.

In rain forests, the majority of plants have very low levels of Cd but the soil is

highly contaminated, containing 6.9 ug/g in a mountain rain forest in Sri Lanka (Jayasekera 1993). The rain forest acts as a Cd trap. All forests act as traps to some degree since they moderate wind and high temperature. Forest fungi can

accumulate up to 687ug/g Cd dry weight (Wondraschek 1993).

Most agricultural soils contain less than 0.1 ug/g Cd. House dust which is 60% biological contains about 6-8 *ug/g* Cd in non-smoking homes impacted by environmental Cd air pollution (Stewart-Pinkham 1991a). Mites, dander, and molds which contribute to house dust can all concentrate Cd making indoor air higher in Cd than outdoor air even in non-smoking homes.

Air, soil, food and water pollutions are interrelated. Air pollution is an especially important input to soil, water, and food since Cd levels in soil and plants are higher at higher elevation and on western slopes that receive more precipitation (Heinerich 1993).

Since Cd is exceptionally bioavailable to algae and fungi, lichens, which are algae and fungi combinations, are a biological trap for Cd air pollution. Using lichens, Sloof (1991) found that the only metal increasing in air in the Netherlands from 1982 to 1987 was Cd and that it was coming from long distance transport, as opposed to local sources of contamination.

A new way of measuring Cd air pollution comes from molecular biology. It involves the detection of genes and gene products that produce Cd tolerance and which are induced in organisms exposed to Cd. In the unicellular marine algae *Thalassiosira weissflogii,* free Cd increases the synthesis of phytochelatin, a metal binding protein found in plants, at the very low threshold of less than 1 picomolar concentration (Ahner 1994). A specific amplification and rearrangement of a gene for a metal

binding protein appeared in bluegreen algae adapted to increasing Cd levels (Gupta 1992).

A Cd resistance protein gene, rapidly induced with Cd exposure in an earthworm, is a possible candidate for biomonitoring Cd input on land (Willuhn 1994). Since all nematodes studied in the Netherlands were tolerant to Cd (Kammenga 1994), detection of genes and gene products that produce Cd tolerance could provide a reasonable index of environmental Cd exposure.

The most important route of human exposure to Cd is active and passive cigarette smoke (Sharma 1983). The Cd in tobacco plants varies with soil pH, and Cd pollution in soil, water, and air. It averages 1.48ug/g in most cigarettes but attains a level of 8.6 *ug/g* Cd in polluted areas in China (Yue 1992).

Indoor air Cd is highly correlated with environmental tobacco smoke concentration (Sung 1991). The sidestream smoke has 5 times as much Cd as the mainstream smoke and five times as much Cd as Pb. In experimental studies with standard cigarettes, inhalation of smoke by mice and rats resulted in 5-6 fold greater levels in lungs and 2-3 fold greater levels in kidneys in exposed as compared with control animals (Gairola, 1991). The concentration of Cd in blood is associated with an index of active smoking and environmental tobacco smoke exposure in adults and children (Willers, 1992).

In animals the organ that contains by far the most Cd is the kidney. The kidney Cd levels are influenced by air pollution (cigarette smoke being especially important in humans), food and water sources

contaminated by Cd, and the redistribution of Cd from the liver to the kidneys that occurs after toxic exposures and during pregnancy (Chan 1993). With overt kidney disease, Cd containing cells are sloughed into the urine, decreasing the levels in kidney cortex. With Cd induction of metal binding proteins, large amounts of Cd can be stored in the kidney without apparent toxicity. Thus, kidney levels of Cd indicate exposure and tolerance.

Kidney Cd levels have been analyzed worldwide and can be used as an approximate measure of global Cd exposure. In a study done in northwest Germany on deceased persons, individual Cd values ranged widely from 0.4 to 94.3 *ug/g* in the kidney cortex. The levels rapidly increased during the first decades of life, plateaued in middle age, and declined after age 70. Non-smokers from a polluted area had a significantly higher level of Cd than non-smokers of the same age from an unpolluted area (Hahn 1987).

In Japan, where the kidney Cd levels have been the highest in the world, the level has increased from 43.95 to 73.47 ug/g in the past decade in spite of a drop in Cd levels in food supplies (Noda 1993). Teenagers have levels approaching those of adults. Kidney Cd levels in penguins from Antarctica vary from 5 to 160 ug/g (Elinder 1992), attributed to their diet of krill. Krill absorb Cd from the water, which in turn receives Cd from air pollution.

On the other side of the world, Cd levels in the kidneys of caribou from the Canadian Yukon, Northwest Territories, northern Quebec and Norway are comparable. The highest level measured was 166 *ug/g* in a 15

year old animal (Gamberg 1994). High levels of Cd were found in the kidneys of red deer from the De Veluw area of the Netherlands (Wolkers 1994). One can conclude that global Cd air pollution, interacting with locally different levels of Cd in background soil and local bodies of water polluted by agriculture and industry, has induced metal binding proteins in kidneys producing high tissue levels.

Exposure assessments are improved when several types of measurements are made. Hair is easily obtained and can be analyzed for multiple elements (StewartPinkham 1989). Hair Cd in children is well correlated with Cd air pollution (Prucha 1987). Hair Cd in newborns of non-smoking mothers was found to be influenced by exposure to a local copper smelter which was polluting the air with 1 ton of Cd /year (Lagerkvist 1992).

When beavers were reintroduced from the Middle Elbe to the Biesbosch, an estuary in the Netherlands contaminated with Cd coming from the Rhine and the Meuse, the average Cd content of their food source was 6.9 *ug/g* (Nolet 1994). The Cd concentration in the kidneys and hair of the beavers correlated with that of the tree bark they fed on. The hair Cd increased three-fold three years after release into the new habitat. The mean Cd kidney concentration more than doubled (24 to 55 *ug/g).* It is very likely that the bark, kidney, and hair Cd levels in this study were influenced by Cd air pollution which was shown in a lichen study to be increasing in air (Sloof 1991).

The standard deviation (SD) of hair Cd was very high in the beavers

which were moved from a setting of low contamination to high contamination; this was also true of the SD of kidney Cd. In animals which were tolerant of a high Cd exposure and were in a steady-state exposure, the hair and kidney Cd levels were high but the SD was low. A high SD in either hair or kidney Cd indicates increasing exposure. The high SD for Cd measured in kidneys around the world infers a *global* increase in Cd exposure.

Mineral Interactions:

Unraveling the multiple, complex, and seemingly contradictory interactions between Cd and other minerals is essential but has inherent uncertainties and complexities. First, there are so many interactions with other metal ions (Blazka 1992). Second, the place of interaction is important. The interaction with Pb dominates affects in the global air, interactions with calcium and Zn are critical in the interface with respiratory, gastrointestinal, and genitourinary surfaces, and interactions with magnesium and calcium have major effects in the intracellular compartments. Third, these interactions affect dynamic processes which are extremely complex, leading to cell proliferation and death, inflammation, and fibrosis. Fourth, some interactions can be inferred but there are no direct studies, i.e. an inverse relationship between lithium, which is lost from the body with stress and Cd ion which promotes the stress. Both interact with sodium, potassium, calcium, and magnesium (Klemfuss 1991). Lastly, geological differences can influence

the effects of global levels of Cd air pollution in complex ways, since deficiencies of minerals or excesses of minerals which create deficiencies allow Cd to have very low dose effects.

A key factor in global Cd air pollution is the level of Pb in air. In a study of Cd levels in heartwood of the oak, Cd levels declined during the period of increasing lead pollution from 1947 to 1970, even though Cd sources of pollution were not declining. After 1970 Cd levels rose abruptly (Hagemeyer 1993). Plants in the areas closest to the source with the highest Pb concentrations exhibited a lower uptake of Cd than areas farther away having less exposure to Pb (Hertzig 1993).

During this period of intense Pb pollution, the global warming trend which began to accelerate in this century, slowed and even reversed itself for a short time (Baliunas 1995). The implication is that Pb, by blocking Cd uptake into plants and back into the atmosphere, blocked a potent global air pollutant that affects global temperature. As we shall see later, Cd's ability to alter biological systems makes this effect scientifically plausible.

Although atmospheric Pb pollution blocks Cd uptake into plants, Pb ingestion increases Cd uptake into animals by 20 percent (Endo 1993). Ingestion of Pb can even increase Cd levels in the brain by breaking down the blood brain barrier (Lockett 1986, Burger 1990, Shuckla 1987). When researchers gave Pb to animals, they assumed the toxic effects they produced were due to Pb. In only the 3 mentioned studies did scientists investigate

effects of Pb ingestion on Cd absorption and uptake into the brain.

Increased Cd absorption occurs in the presence of low dietary intake of iron and calcium and exposure to cigarette smoke (Kowal 1988), conditions associated with increased blood Pb (coyer 1990, Rooney 1994). Blood Pb has been assumed to be a marker of exposure to Pb when, in actuality, it serves as a marker of Cd absorption, as well.

While leaded gasoline use can bind up Cd in air possibly decreasing global warming, Pb ingestion coming from leaded gasoline use increases

Cd uptake into the brain where it has highly toxic effects (StewartPinkham 1989b). In equimolar doses the two metals can mutually cancel each other's individual effects (Nation 1989). There is a range of synergistic and antagonistic actions between Cd and Pb producing multiple, confusing, and contradictory effects.

At the molecular level, there appears to be a Cd-sensitive cell receptor that interfaces with viral proteins, cancer proteins, and compounds associated with inflammation that Zn (2+)> Cu(2+)>Pb(2+) can block (Smith 1989). Cd activation can produce hormone-like signals which increase free calcium in the cytosol and quickly activate gene transcription (Smith 1994). Animals exposed to endotoxin, a glucocorticoid, and Pb all survived, while when exposed to these conditions together with Cd they all died (Cook 1974). It appears that in stress situations, simulated by the glucocorticoid, a low dose of Pb may have a *beneficial* effect by modulating the stress response

controlled by this Cd receptor. Other indications of a beneficial effect from Pb come from feeding experiments (Schroeder 1964) in which a low dose of Pb fed to mice and rats resulted in the female animals outliving the male animals. In this century, women started outliving men in industrialized countries using leaded gasoline.

The interactions between Cd and zinc (Zn) are particularly critical on this cell surface receptor that influences inflammation and carcinogenesis. Zn levels in air are falling as measured in lichens (Showman 1989). This could come from a Cd-induced decreased uptake of Zn into plants and subsequent release into air. With increased dietary Cd there is decreased Zn absorption (Coppen-Jaeger 1989). With immune activation there is enhanced urinary excretion of Zn (Melichar 1994). Multiple conditions can therefore make a plant or animal more susceptible to effects of Cd air pollution by producing Zn deficiency.

Metallothioneins (MT), low molecular weight binding proteins found in animals, are induced by Cd and Zn. One promotor for MT responds only to Zn and another responds to either Cd or a glucocorticoid (Takeda 1994). Cd has 40 times more affinity than Zn for the DNA zinc finger binding site for the glucocorticoid receptor (Freedman 1988). In stress situations, serum Zn levels are low, enhancing the effects of free Cd ions. This suggests that Cd rather than Zn has a physiologic role in stress responses. Zn (more than Pb), by blocking the Cd receptor proposed by Smith, modulates the stress response by inhibiting the Cd-induced increase in

free intracellular Ca. The Cd-Zn antagonism is known to affect DNA repair (Nocentini 1987), hypertension (Schroeder 1975), birth defects (Hartsfield 1992), and carcinogeneisis (Oldiges 1989).

Zn and Cd have antagonistic effects in inflammatory processes. An enzyme present on the membranes of neutrophils breaks down substance P, a chemical mediator of pain, and other inflammatory peptides. With stimulation of the Cd receptor, this enzyme disappears from the surface, effectively increasing inflammatory signals (Shipp 1991). By blocking Zn absorption, enhancing Zn excretion or indirectly inhibiting an enzyme, Cd increases the potencies of inflammatory peptides.

The mineral balance, rather than dose alone, dramatically influences effects. There is a calcium and Zn containing enzyme that is a critical step in apoptosis, programmed cell death, in which cells die without stimulating inflammation (Lohmann 1993). Cd can take the place of calcium and stimulate apoptosis or take the place of Zn and block apoptosis. Generally, Zn protects the cell from Cd cytotoxic effects, but sometimes a cytotoxic effect is helpful. With high doses of Cd causing Zn deficiency, Cd appears to exert a cytotoxic effect on spontaneous and chemically induced cancers in mice (Waalkes 1991), thus functioning as an anti-carcinogen.

Catecholamines, chronic stress, caffeine and other
p sychostimu I ants increase magnesium excretion in the urine. Insufficient stomach acid decreases the absorption of both magnesium

and Zn. Areas with high calcium and low magesium in soil and water can lead to tissue magnesium depletion.

All these variables can lead to intracellular magnesium deficiency which increases free cytosolic Cd ions (Quamme 1992), producing injurious oxidation of cell membranes (Manta 1991). Magnesium deficiency in rats leads to an early peak in substance P, which in turn stimulates chemical mediators of inflammation (Weglicki 1991). Chronic Cd exposure by depleting both Zn and magnesium can increase inflammatory signals in an acute illness or following trauma but have little effect in a steady state unaffected by stress or nutrient deficiency.

Cd has many interactions with calcium. It has 1,000 times more affinity than calcium for an enzyme which pumps calcium out of the cell (Verbost 1989). While extracellular calcium decreases Cd absorption, free intracellular Cd increases intracellular calcium, an important second messenger. Feeding Cd to calcium-deficient, estrogen- deficient or vitamin D-deficient animals increases fecal calcium loss by directly stimulating bone resorption (Sacco-Gibson 1992). Evidence that air pollution with Cd can cause this effect comes from a bone density study of female twins in which the heavier smoker of the twin pair showed evidence of bone resorption and significant reduction in bone density (Hopper 1994).

In addition to inducing losses of calcium, magnesium, potassium, and Zn, Cd can conceivably lead to lithium losses. Lithium is associated with mood stability (Lehmann 1994). Hair lithium levels which were once low (< 0.04 *ug/g)*

in 20% of American samples nationally are now low in close to 80% of samples in my community, which has been heavily affected by Cd air pollution from a large waste incinerator plant for the past 10 years.

Although there are no direct studies of Cd effects on lithium, lithium has many interactions with hormones, vitamins, and ions affected by Cd (Klemfuss 1993). There are a string of associations that link Cd toxicity with lithium losses: 1. lithium excretion is enhanced with increased aldosterone levels (Strazzullo 1994), a Cd effect (Webb 1977), 2. obesity, which has been increasing around the world, is associated with magnesium deficiency (Durlach 1993) and increased lithium excretion (Reiss 1994), 3. Cd exposure induced violence in dogs (Friberg 1971) and low levels of lithium and cobalt (from B-12) in scalp hair (Schrauzer 1992) are associated with violence in humans, and 4. both lithium deficiency and Cd toxicity are associated with low birth weight, reproductive failure, and decreased life expectancy (Anke 1991, Nolet 1994).

Cobalt, nickel, iron, and manganese can all stimulate the Cd cell surface receptor and therefore can be expected to have synergistically toxic effects with Cd. Cd, cobalt, and nickel produce similar malformations in the frog, suggesting they could be acting through the same mechanism (Plowman 1994). Cd, nickel, and chromium are all elevated in patients with lung and coloectal cancer (Martin Mateo 1990).

Antagonism and synergism

were found between Cd and mercury, copper, and iron. Mercury can displace Cd from binding proteins (Funk 1987), leading to an increase in free Cd. Copper can also displace Cd, producing toxic effects, but, like Zn, it can competitively inhibit Cd uptake (Endo 1993, Blazka 1992) and block the Cd cell surface receptor (Smith 1994). The interactions of Cd and iron are complex and vary with age of the host and oxidation state of the iron. Oxidized iron increases the toxicity of Cd (Sakata 1988).

An excess of one mineral can produce a deficiency in another mineral and a deficiency in one mineral can produce an excess in other minerals. Excess selenium intake inhibits copper and sulfur metabolism making the organism more sensitive to Cd toxicity, but equimolar quantities block the toxicities of the two substances (Webber 1985). Rats fed Cd and a low selenium diet developed increased iron and copper levels in their eyes (Jamall 1989). Problems associated with iron excess and copper excess could be exacerbated by exposure to Cd in a setting of selenium deficiency.

There are large areas of the world with selenium deficiency that can be expected to have heightened sensitivity to Cd air pollution, including large areas of the former USSR (Ermakov 1992), parts of China, Yugoslavia (Maksimovic 1992), and Christchurch, New Zealand (Sluis 1992). Areas of geological mineral excesses or deficiencies are more vulnerable to toxic effects of Cd at a given level of exposure.

The ability of multiple

minerals to act synergistically or antagonistically in the stress response makes it impossible to determine the effect of Cd based on the dose of Cd. Calcium, magnesium, sodium, potassium, Zn, copper, manganese, iron, selenium, nickel, chromium, molybdenum, germanium, arsenic, mercury, and aluminum are minerals that are known to affect Cd. Lithium can be inferred to interact with Cd. Boron, vanadium, silicon and other trace metals may well have interactions with Cd that are significant.

It is quite possible that many studies involving metals may have a hidden effect through a change in ambient

Cd uptake, since it has such a very low threshold for effects and can enter the cell through multiple channels. We have seen that Pb ingestion can increase Cd uptake into the brain. Aluminum, also, increases Cd absorption (Sugawara 1993) and increases tumors (Schroeder 1975), although very little of it is absorbed. It is reasonable to hypothesize that Cd absortion caused by aluminum ingestion increased the tumors.

Around the world, differences in the minerals in the soil, water, and food affect the uptake and toxicity of Cd air pollution. By multiple mechanisms, Cd affects all cells, globally, impacting weather and climate. A comprehensive and highly individualized approach is necessary in addressing local environmental pollution effects and understanding responses of humans to metals. Because of these complexities, it is particularly difficult to identify controls when attempting to detect impacts of Cd air pollution on environmental

problems like forest declines or changes in human health (StewartPinkham 1991).

Chemical Interactions:

Cd is unique among metal ions in its ability to affect the metabolism of organic chemicals. Its effects are influenced by co-exposure to many chemicals in the environment, food, and pharmaceuticals. In an interaction study of the effects of intratracheally instilled nickel chloride, cobalt chloride and Cd chloride with [3H]benzo[a]pyrene injected into the arterial circulation of rat lungs, Cd alone significantly affected its metabolism (Williams 1984). So, although these other metals can substitue for Cd at the cell surface receptor, they do not influence the metabolism of chemicals the way Cd does. Polluted sediments contain organic compounds and Cd. A dose response relationship was found between Cd concentration and metabolic activation of benzo[a]pyrene and other carcinogens (Rodriguez-Arita 1994).

Since air pollution is always mixed, the effects of organo-chlorides and other toxic compounds cannot be separated from the co-exposures to Cd. Many of these substances like dioxins, pesticides and herbicides bind to the estrogen receptor (Thornton 1993). Estrogen increases the uptake of Cd into the liver, mammary glands, and kidneys (Nishiyama 1988). Cd can increase blood lipid levels, raising the levels of fat soluble chemicals in the rest of the body (Leonzio 1992). By increasing tissue pesticide levels, Cd exposures can result in fewer conceptions and more frequent spontaneous abortions (Gerhard

1992). Thus, indirectly, Cd can exert dramatic effects by altering the levels of organic chemicals.

Cd and organic compounds can work synergistically in producing a toxic effect. A dosage of an organophosphorus compound and Cd, that induce minor changes when given separately, together damage the liver and kidney in 24 hours (Chishti 1993). Co-exposure of low dose Cd and other chemicals can produce malformations and cancer (Yamada 1993, Saxena 1986, Wade 1987). Although PCB's and Aroclor 1254, a pesticide, did not initiate tumors as Cd did, they potentiated the tumorigenic effects of low dose Cd (Tehseen 1992, Schaeffer 1991).

Cigarette smoke is a major source of exposure to Cd and multiple toxic organics. Cigarette smoking increases the risk of alcohol abuse. Alcohol consumption plays a major role in Cd uptake from the GI tract and accumulation in tissues. By increasing losses of Zn and magnesium in the urine and increasing free Cd ions in cells, it enhances the effects of Cd, reflected in oxidative damage (Sharma 1991,1992). Cd exposure makes rats prefer alcohol to water (Nation 1987), suggesting that the Cd content in the cigarette smoke is principally responsible for the increased risk of alcohol abuse.

Lithium deficiency, which can be aggravated by Cd-induced increases in aldosterone, is associated with hard drug use (Schrauzer 1991). Thus, directly and indirectly, Cd has an impact on multiple

forms of substance abuse. In the United States, use of tobacco, alcohol, and other drugs is associated with the leading causes of morbidity

and mortality: motor vehicle crashes, homicide, suicide, cancer, lower educational achievement, and school drop out (MMWR 1992).

Countering this toxicity is the nutritive value of food. A nutrient dense, high-fiber, plant-food diet with adequate protein and fish oils is the most protective against experimental Cd toxicity (Webb 1979). The B-complex, anti-oxidant vitamins and minerals, bioflavanoids, fiber, essential fatty acids, and the fat soluble vitamins are all protective in unique ways (Grimble 1994, Stewart-Pinkham 1991b). Also, herbs and spices that are used in various cultures as medicinals or flavorings counter toxic effects of Cd.

Cd, itself, which may be present in some of these herbal remedies, can have a beneficial effect. Although low doses that would come from air pollution promoted cancers, high oral doses of Cd, 1,000ppm (the approximate amount in certain fungi), have been found to block chemically initiated and spontaneous tumors in the lungs and liver of mice (Waalkes 1991a).

With our current highly processed diet, devoid of essential nutrients and adulterated with pesticides and other chemicals, individuals exposed to Cd air pollution and environmental toxic chemicals or cigarette smoke are vulnerable. Because Cd affects the metabolism and tissue deposition of many chemicals, including environmental pollutants and pharmaceuticals, Cd air pollution can interact with locally specific chemicals, increasing their toxic impacts on the liver and kidney. These combinations can also cause birth defects or cancer. In addition,

Cd exposure in humans can lead to substance abuse and the societal violence, morbidity, and mortality associated with their use.

Biologicals:

The extreme sensitivity of cells to Cd makes global Cd air pollution so potent even though the exposure is at a low level. Bacteria exposed to Cd have a respiratory burst, increasing the production of carbon dioxide and water, two greenhouse gases associated with global warming. With gradual exposure to Cd, tolerance can develop through induction and modification of genes that produce either pumps to exclude Cd or binding proteins to detoxify it within the cell.

These adaptations can have complicated effects. Cd can increase production of pigments in marine algae, causing more light to be absorbed, thus warming the ocean. It is plausible that these effects could influence the southern oscillation and "el nino," affecting weather patterns around the world, which in turn produce droughts, floods, and the decline of salmon in the Pacific Northwest.

Cd is toxic to trees, inhibiting roots, decreasing nutrient uptake, decreasing photosynthesis and increasing photorespiration which also increases water and carbon dioxide production (Stewart-Pinkham 1991a). By making trees vulnerable to injury and disease, Cd promotes forest declines, further increasing global warming.

Cd tolerant organisms do better in an environment with Cd, while Cd sensitive organisms are adversely affected. The seasonal changes in Cd pollution lead to

intermittent stress for both types.

When bacteria acquire plasmids for Cd resistance they usually develop multiple drug resistance as

well. The gene for Cd resistance in yeast is very similar to the gene for multiple drug resistance protein (Szczypka 1994). This gene is found in cancers resistant to chemotherapy. Inducing Cd tolerance in cancers and bacteria has a negative impact on human health.

With the HIV epidemic arriving in the time period of falling Pb pollution and rising Cd pollution it would be most helpful to know whether Cd played a role in the progression of HIV to AIDS. There is a body of circumstantial evidence that suggests this to be true, in that many of the substances that block Cd toxic effects, or enhance its excretion, also block the replication of HIV (Stewart-Pinkham, 1991b). Although no studies have been conducted to test this hypothesis directly in a laboratory setting, studies have been done on Herpes simplex virus, a chronic virus that is activated in a variety of stressful circumstances.

Cd is the only metal that activates Herpes simplex from a latent state (Fawl 1993). Continued administration of Cd increases the yield of infectious virus by 10 to 100 fold and prolongs the recovery of infectious virus from 6 to 11 days. It is noteworthy that Zn, nickel and manganese block the Cd-induced infectious virus. Likewise, lithium blocks Herpes activation (Skinner 1980).

There are many unanswered questions regarding Cd's interactions with biologicals. Since Cd exposure induces tolerance in bacteria, a

process associated with plasmids where virulence factors are encoded, is it possible that chronic Cd air pollution is increasing bacterial virulence? With virulent strains of Streptococcus gaining attention it would be important to know if it is inhibited by Pb and promoted by Cd. From 1968 to 1983 the rate of Streptococcal- induced Rheumatic Fever in the industrial world exposed to lead pollution was very low and then it rose again for unknown reasons.

In studies of metal ion air pollution and a bacterial infection, Cd was the most toxic of all the metals, causing 100% mortality in the mice (Gardner 1977). However, with influenza, a viral infection, Cd exposure increased host resistance by increasing the supply of phagocytic cells into the lung (Chaumard 1991).

Multiple factors could influence the outcome of influenza virus in a host. What would happen if the influenza virus had Cd already bound to its nucleic acids? Could it replicate and mutate more rapidly? Perhaps a virus with attached Cd would cause more irritation to the respiratory tissue. There is evidence that Cd plays a role in the toxic effect of respiratory syncytial virus in that passive smoke exposure increased hospitalizations for this viral illness in Perth Australia (Reese 1992).

Timing could be critical. Cd administered before exposure to ionizing radiation sharply decreases lung inflammation; when given together with radiation, the two synergistically increase lung inflammation (Salovsky 1993). Such complex, bidirectional responses could occur with co-exposure to Cd

and other biological stressors.

The human host has a large reservoir of bacteria and fungi in the gastrointestinal tract. If these bacteria are "friendly" they provide nutrients for the host and protect the integrity of the gastrointestinal barrier so that tight junctions are tight and substances that pass through to the blood stream go through cells and not between them.

With the use of antibiotics, however, these "friendly" bacteria can be lost and replaced with bacteria and fungi that exert a toxic effect in the micro-environment near the intestinal lining cell, breaking down the tight junctions connecting them, allowing foods, drugs and chemicals to activate immune cells in the submucosa.

The constituents of diet have a strong influence on the growth of bacteria and the uptake of Cd from the diet. Cd in human food is very well absorbed compared to Cd in rat chow (Anderson 1992). This difference has been linked to fiber in the diet and fiber strongly influences bacterial flora.

There is much that is unknown regarding Cd's effects on biologicals and the impact of increasing global Cd air pollution on the global environment and human health. Because these impacts are of such potential importance, follow up studies are urgently needed. At the present, there is suggestive evidence that Cd can contribute to global warming, increase the virulence of disease, and make cancers resistant to treatment.

Biochemical and Molecular Studies:

In contrast to other toxic metals of concern like Pb and mercury, Cd is actively taken up by cells with fluid membranes and transported in plants and animals to distant sites where it readily affects multiple targets, producing a great number of effects (Friberg, 1971, Webb 1979, Foulkes 1986, Nordberg 1992). In a direct comparison of the toxicity of 11 metals, using reduction of oxygen consumption and deep body temperature as end points, Cd was the most toxic element followed by mercury, nickel, cobalt, copper, Zn, magnesium, manganese, Pb, and last aluminum (Gordon 1990). In this study Cd was 200 times more toxic than Pb and 20 times more toxic than mercury. In a study of 16 metal ions by Lag (1987), using a tracheal organ culture, Cd was the most cytotoxic at the lowest dose, paralyzing all the cilia and killing 90 % of the cells at a dose of only 10 uM. Whereas Pb, at a dose as high as 200 uM, had virtually no effect on the cilia or the viability of the cells. This toxic potential of Cd is important because with environmental pollution and human disease it is often present in low dose, compared to other metals and chemicals, but can still have a highly significant effect (Pool-Zobel (1994).

Although in the past Cd was considered a purely toxic metal ion with no essential function, this highly toxic metal ion appears to have been harnessed by the cell to play an essential role in the stress response. By stimulating the Cd sensitive cell surface receptor it acts as a first messenger of stress. By

uncoupling oxidative phosphorylation in mitochondria by blocking 2 sites (Miccardi 1993), it depletes the cell energy supply, and generates free radicals which cause oxidative stress. By moving into the nucleus and activating gene transcription, Cd, like Ca(2+), acts as a second messenger, producing stress proteins and turning off the normal housekeeping genes.

When Cd is instilled in the trachea of rats, acute phase response proteins are induced in the liver of the animal (Frankel 1991).

Oxidative stress occurred in all tissues tested in animals exposed to 25 ug Cd /Kg (Manta 1991). Lungs and brain were the most responsive. This oxidative stress can have no apparent effect or increase the vulnerability of tissues like the gastric mucosa to ulcers (Oner 1994) or cause cancer (Koizumi 1992).

The stress response is an adaptive mechanism to deal with change. It rids the body of damaged cells, viruses, and cancerous cells. However, if these cells develop Cd resistance they can persist and cause disease. Thus, Cd can be both beneficial and detrimental. Cd exposure can protect the lung from influenza (Chaumard 1991), oxygen toxicity, and radiation damage (Salovsky 1993). But it can be immune suppressive and increase the virulence of disease. With its direct toxicity and immune suppressive effects it is likely to promote disease outbreaks in an unpredictable manner (Sovenyi 1993).

Although many stimuli trigger the stress response, the most potent are emotional stresses (Hidalgo 1987). No matter what the stress, nutritional status is extremely

important in modulating the response. In a state of Zn deficiency the cell surface receptor can be too easily triggered. In a state of magnesium deficiency the uncoupling and free radical formation becomes a problem. Although with adaptation free Cd can be bound, turning off the stress signals, mutations in gene products cause persistent sensitivity to its toxic effects, as in cystic fibrosis (Szczypka 1994). It is possible that many genetic diseases will be found to be caused by Cdinduced gene amplifications or Cdinduced mutations that decrease Cd tolerance of specific cells.

Cd has complex hormonal effects mediated by a staggeringly complex number of chemicals. In addition to activating the hypothalamic adrenal axis (Hidalgo 1987), it activates cyclo-oxygenase releasing prostaglandin E2 (PGE2) which plays a role in bone resorption (Miyahara 1992). Both effects are stimulated independently by interleukin-1, a cytokine secreted by immune cells (O'Connell 1994). Prostaglandins are biological mediators linked to inflammation and immunity with helpful and harmful effects.

Cd has such a multiplicity of effects in part because it affects multiple ion channels (Schoenmakers 1992). Cd triggers cytotoxic actions by disrupting ionic balances across membranes (Koizumi 1994a). In conditions of acidosis, which Cd exposure can induce, Cd is very toxic to mitochondria, while it is without effect at a neutral pH of 7.4 (Koizumi 1994b). Lithium may antagonize a toxic effect of Cd on cells by promoting alkalinization of the intracellular space (Munsch

1994).

In experimental studies with Cd, multiple enzymatic changes were observed when no morphologic effects were found (Wloch 1992b). In another study, Cd exposure had effects that can enhance susceptibility to disease but didn't change fetal weight or birthweight (Hazelhoff-Roelfzema 1987). In normal appearing Cd exposed embryos, the number of cells in critical tissues of the brain, eye, ear, extremities and glandular tissue were lowered (Canning 1987). The effects of Cd exposure can be quite subtle and difficult to prove.

Global Cd air pollution, by increasing the cellular content of Cd, can promote an over-reaction to stress stimuli that can lead to nutrient depletions and maladaptive responses in a complex and unpredictable fashion. Cd's effects at low dose are highly variable depending on age, gender, species, multiple genetic factors, route of exposure, *prior* nutritional history and exposure to Cd and other stressors, and *current* nutritional history and exposure to biologicals (viruses, bacteria, fungi, and parasites), toxic metals (Al, As, Cr, Hg, Ni, Pb), organic compounds and other stressors (pH, temperature, radiation, trauma, and psychosocial stress).

The consequences of chronic stress are multiple alterations associated with premature aging. Magnesium deficiency is thought to cause immunosuppression, muscle atrophy, central obesity, osteoporosis, hyperglycemia, hyperlipidemia, and atherosclerosis (Durlach 1993). Zn deficiency, a Cd toxic effect, causes many problems associated with aging

(Bin 1994). Dehydroepiandrosterone (DHEA), which increases feelings of well being, improves the quality of sleep, increases stress tolerance, and decreases bone loss (Morales 1994), declines linearly until death after age 20. Cd may act on the adrenal to cause its decline, directly or possibly through depleting the adrenal of lithium, since supplemental nutritional lithium has effects similar to those produced by DHEA (Schrauzer 1994).

In spite of the complexity of the stress response and the mediators that trigger interlocking actions, modulating its effects, it is at a biochemical level that Cd's actions are most clearly delineated, even though they are difficult to predict because of the large number of variables that have an influence. Oxidative stress, acidosis, decreased mitochondrial function, vitamin and mineral imbalances, glandular dysfunction, and a myriad of stress responses, including elevated interleukin 1 and prostaglandin E2 are some of the biochemical effects arising from Cd toxic effects.

Epidemiological and Observational Studies:

Epidemiological studies, using blood and urine Cd, were unable to find effects in a community contaminated with Cd, Pb, and Zn (Morgan 1988). Blood Cd levels can vary four fold in a day (Vahter 1992) and do not necessarily correlate with blood Pb (Berglund 1994) or toxic effects of free Cd ions. Although Cd can produce hypertension in animal models (Schroeder 1967), most studies that look for correlations with blood and urine Cd do not show

a linear correlation with hypertension (Staessen 1990, 1992,1993). However, in one case-controlled study of non-occupationally exposed males with mild stable untreated hypertension, blood Cd was higher in the hypertensives vs the normotensives with a more significant difference in the nonsmokers (Vivoli 1989). Alcohol, by increasing Cd uptake and depleting Zn, would be expected to cause hypertension and that was found in a study done in Japan (Watabayashi 1994).

Instead, blood Pb has been correlated with hypertension, neurologic impairments, osteoporosis, and renal cancer in epidemiologic studies and ingestion of Pb produced some of these effects in animal studies. Pb met the Hill criteria used to prove causality (Goyer 1993). In a group of individuals with the same exposure to Pb in the environment and food, the blood Pb will be consistently higher in individuals with genetic suceptibility to toxic effects of Cd, a poor diet, or increased levels of stresses of any kind from Cd-induced resorption of bone where Pb is stored, increasing blood Pb. Relative increases in blood Pb measure a toxic effect of Cd rather than increased **Pb** exposure (Stewart-Pinkham 1989b).

Observational studies are revealing of the kinds of effects one might expect from Cd air pollution. Two such studies involved exposure to Cd and nickel in battery factories. In one 63% of individuals exposed to Cd fumes had sinus x-ray abnormalites compared to 33 % in the general population (Shaham 1993). In the other approximately 5 % of the employees complained of a

variety of symptoms: headache, weakness, fatigue, lassitude, dizziness, skin eruptions, gum disease, tooth loss, caries, nasal congestion, nose bleeds, inability to smell, cough, phlegm production, wheezing, shortness of breath, "asthma", bone pain, urinary frequency, kidney stones, sterility and multiple abortions. One patient died from an amyotrophic lateral sclerosis like illness, 6/38 had brain atrophy by CT scan, one died of lung cancer, one died of pancreatic cancer, and one died of leukemia (Bar-Sela 1992). Similar symptoms were found in a community exposed to volatile organic fumes (Ozonoff 1987). These studies illustrate the wide variety of symptoms and diseases Cd exposures can produce with other substances that cause synergistic toxicity.

A particularly significant observational study, discussed in the section on exposure, involved the transfer of beavers from an unpolluted area in Germany to a polluted area in the Netherlands impacted by Cd air pollution (Sloof 1991). These beavers had the lowest population growth of released beavers in Europe (Nolet 1994). Thirty percent of the animals transferred were found dead of disease, suggesting that they were experiencing toxic effects in their new environment. They had not developed Cd tolerance. Beavers from a polluted area in Germany, averaging 467 u/g Cd in the kidneys (the greatest reported in herbivores), had the highest fertility. Their mortality rate was 15% and due to traffic fatalities rather than disease. The animals in this highly contaminated area were adapted to Cd.

A comparison of gonadal levels of Cd in beavers from these two sites would be most interesting to check, since in a contiguous area in northwest Germany, rabbits are experiencing reproductive failure, associated with elevated Cd in their gonads (Lutz 1993). Cd air pollution could affect reproduction by depleting lithium, a possibility which could be checked by analyzing hair or adrenals for lithium. By breathing in Cd, the olfactory bulb of the animals can be affected through a direct nasal exposure (Evans 1992). Inability to smell could affect sexual behavior without even affecting gonadal Cd levels.

In the past the evidence that Cd was having a toxic effect at ambient levels of exposure was rejected because of inconsistencies, confounding factors, lack of dose response relationships, and a failure to find correlations with blood, urine, and hair Cd levels. Blood Pb, on the other hand, which is increased by Cd toxic effects, is correlated with the problems Cd is known to cause experimentally.

Observational studies from exposures to Cd and other substances, known to have a synergistic effect, indicate that exposed individuals can have complex symtoms, signs, and disease processes that share much in common with Chronic Fatigue and Fibromyalgia, the new morbidity affecting growing numbers of women and young adults (Stewart-Pinkham, 1990a). The findings of reproductive failure, disease, and decreased life span in animals exposed to increasing levels of Cd in the Netherlands suggest that increasing exposure to Cd air pollution could

have a detrimental effect in humans and trees that are not adapted to Cd or genetically cannot tolerate increased exposures.

Conclusions:

Using the precautionary principle, the weight of evidence presented supports the following conclusions:

Population growth and decreased use of leaded gasoline has increased global Cd air pollution, while cigarette smoke contributes heavily to Cd exposure in humans.

Genes and gene products producing Cd tolerance in cells respond to Cd exposure in a dose response manner. A high SD in hair and kidney Cd levels indicates exposure in group studies.

Cd has complicated interactions with other metal ions. Additions of metal ions, like Pb and aluminum, can increase Cd absorption and lead to Cd toxic effects. A comprehensive and highly individualized approach is needed in order to understand effects of metals. Meaningful control groups are virtually impossible to obtain.

Plants and animals use this highly toxic metal ion in the stress response to rid themselves of damaged, infected, and cancerous cells. However, in combinations with other chemicals and toxic metals and in a nutrient deficient state, Cd can cause reproductive failure, birth defects, infections, multiple organ damage, premature aging, substance abuse, societal violence, and cancer.

There is suggestive evidence that through effects on biological systems, Cd contributes to global warming, forest decline, increased virulence of disease, and cancers resistant to treatment.

Blood Cd levels do not generally indicate a toxic effect of Cd, but blood Pb elevations in groups having a toxic effect do. Observational studies document responses that share many characteristics in common with those found in individuals suffering from Chronic Fatigue.

Implications:

Using the precautionary principle, it makes sense to limit the exposure of the planet and humans to increased quantities of Cd air pollution, especially when Pb pollution is radically reduced. To protect the environment and public health we need to minimize the sources of Cd air pollution. Limiting global population growth would directly limit Cd air pollution.

Another strategy is to sequester Cd. This can be done biologically by preservation of forests, especially the complex ecosystems in rain forests, which protect the entire planet from the stress of increased Cd exposure.

Bio-technology can be used to sequester metals and break down organic pollutants (Raraz 1995). All stacks of power plants and large factories could be fitted with electrostatic precipitators to remove particulates and a water trap with biological filters to remove Cd and Hg and harmful volatile organic compounds. These preventive measures require and deserve worldwide governmental support. Hazardous waste sites should be treated with minerals that form insoluble precipitates and organic compounds should be biologically degraded.

The effort to stop pollution at its source should be continued. Applying chemicals to one's lawn, when this exposure could be adversely affecting one's neighbor, should be as unacceptable as smoking in public. Collectively, we need to protect our environment from an onslaught of chemicals, even though only a minority may be showing adverse effects.

An obvious way to decrease human disease from Cd is to limit the allowable level of Cd in cigarettes. Low levels of Cd in cigarettes do not cause inflammatory effects (Lai 1992). Since tobacco is a very large industry world-wide with heavy government subsidies, it makes sense to require farmers to grow the tobacco under conditions that limit Cd uptake. It is possible that strains of tobacco that do not accumulate Cd could be developed. Although there are mulitple carcinogens in tobacco, this single step would greatly decrease the toxicity of cigarette smoke, both active and passive.

Education is necessary to motivate the public to avoid the use of tobacco, alcohol, drugs, and a bad diet and so reduce the incidence of disease. Parents must not expose their children to cigarette smoke. Teenagers need to know that cigarette smoking, alcohol use, illicit drugs, and a poor diet will adversely influence their health as they age and increase the risk of having children with birth defects. Certainly we all have a responsibility to minimize genotoxic effects resulting from our life style.

There are many conditions including HIV infection and cancer that are not responding well to current medical management. Rather than looking for answers from well conducted double blind trials, patients need to be evaluated biochemically in a comprehensive manner. By supplementing deficient nutrients, like magnesium, Zn, and lithium, addressing life style issues, including diet, exercise, and emotional stress, physicians can help patients adversely affected by current levels of pollution.

Traditional medicines in use for centuries, like licorice, garlic, and fungi, have significant effects on Cd or contain Cd. These medicines should be studied for their mineral content and effects on Cd in freshly biopsied cells, rather than in cell lines that have already acquired Cd resistance.

The lesson one learns from studying the effects of Cd air pollution is that biological changes are interconnected. Diseases in wild life, decline of forests, "el nino," severe flooding, global warming, societal violence, the HIV epidemic, cancer, and chronic fatigue are influenced by many factors, but they are all affected by Cd air pollution. Cd acts as a "chaos" factor, so increasing changes could occur which might not provoke concern until a sudden failure of adaptation causes a disappearance of individual species, and even the collapse of eco-systems (Stewart-Pinkham 1990b).

This global factor is amenable to control; therefore, in these final 5 years of the twentieth century, scientists must collaborate in a new kind of interdisciplinary science to reduce the harmful impacts of Cd air pollution. A scientific, molecular-based study of all disease, using the hypothesis that free Cd can have

many effects on cell processes in genetic and acquired disease, is both feasible and desirable.

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