THE LINKAGE OF GLOBAL ISSUES WITH CELLULAR EFFECTS OF CADMIUM AIR POLLUTION

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Abstract:

According to ''the precautionary principle,'' 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 which will protect our ecosystem. This paper uses this guideline to assess the effects of cadmium exposure and its toxicity. This highly toxic metal is apparently used by the cell in the stress response to get rid of damaged, virus-infected, and cancerous cells. Indiscriminant exposure to global cadmium air pollution alters the cellular content of free cadmium ions and the minerals that antagonize its effects, affecting the response of cells, organs, and individuals to all other stimuli. Cadmium's effects at low dose are thus influenced by many factors, not just dose. These factors include age, gender, species, genetic factors, *prior* nutritional history and exposure to cadmium and other stressors, and *current* nutritional history and exposure to other stressors. Other toxic metals, organic compounds, biological pathogens and emotional stresses interact with cadmium to produce effects. Stress effects at a cellular level appear linked with current global problems affecting the environment, such as global warming, and human health effects, like the increase in disabling fatigue and infectious disease.

We need to make use of the beneficial effects of cadmium while decreasing harmful effects of cadmium air pollution by limiting exposure to active and passive smoke, preserving forests, using biotechnology to reduce air and water pollution, and reducing the output of chemicals. Moreover, a molecularly based study of disease, using the hypothesis that free cadmium ions affect cell processes in genetic and acquired diseases, will improve the way patients are evaluated and treated for such varied complaints as chronic fatigue, cancer, HIV infection, substance abuse, and reproductive failure.

Introduction:

Global problems have been difficult to study scientifically because they are affected by so many interdependent variables. However, because of the critical importance of our global problems, we can no longer afford to ignore what we cannot thoroughly know (Funtowicz 1994). New problems demand new forms of problem solving. Just as particle physics eluded measurement by Newtonian theory, evaluating global processes affected by cadmium air pollution

requires a new approach that can deal with inherently unresolvable uncertainties and complexities.

Using conventional approaches lead and mercury have been identified as major environmental pollutants of concern. Yet, in a direct comparison of the toxicity of I I metals in rats, using reduction of oxygen consumption and deep body temperature as end points, cadmium was the most toxic element followed by mercury, nickel, cobalt, copper, zinc, magnesium, manganese, lead, and last aluminum (Gordon 1990). See Figure below.

In this study cadmium was 200 times more toxic than lead and 20 times more toxic than mercury. In a study done by Lag (1987), using a tracheal organ culture, cadmium was the most toxic of 16 metal ions, paralyzing all the cilia and killing 90 % of the cells at a dose of only 10-' M. Lead, in contrast, at a higher dose of 2 X 10' M, had virtually no

effect on the cilia or the viability of the cells. This toxic potential of cadmium is important because it is present in environmental pollution and human disease at a low dose, compared to other metals and chemicals, yet still has a highly significant effect (Pool-Zobel (1994).

Historical Perpective. Although cadmium is a very toxic metal, cadmium air pollution has not yet been recognized as the major environmental and health threat that it is. Scientists who use conventional epidemiological approaches have found it difficult to agree on the extent of

cadmium exposure from air pollution and effects solely attributable to cadmium. Scientists have been reluctant to implicate cadmium in any major health or environmental issue.

Three assumptions have dominated studies of cadmium effects in humans. First, that since exposure to cigarette smoke was a mixture of pollutants, toxic effects from cigarette smoke could not be attributed to cadmium. Second, that the kidney was the target organ and toxic effects occurred at high levels of cadmium associated with industrial exposure. Third, that air pollution was an insignificant source of cadmium, aside from cigarette smoke.

Researchers expected increasing cadmium exposure to increase blood, hair, and kidney levels. That is not the case.

Increasing exposure increases the SD of hair and kidney levels (Nolet 1994). Consequently, researchers failed to find proof that cadmium was the cause of any human disease, except in industrial exposures or unusual environmental contaminations. Instead, other metals like lead, mercury, copper, aluminum, chromium, and nickel have received a great deal of attention in spite of their limited direct toxic effects documented in the Gordon study.

Using blood and urine cadmium levels, scientists were unable to find correlations with adverse health effects in a community contaminated with cadmium, lead, and zinc (Morgan 1988). Blood cadmium levels can vary four fold in a day (Vahter 1992) and are not directly correlated with toxic effects of free cadmium ions. Although cadmium can produce hypertension in animal models (Schroeder 1967), most studies that look for correlations with blood and urine cadmium 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 cadmium was higher in the hypertensives vs the normotensives with a more significant difference in the non-smokers (Vivoli 1989).

Alcohol, which increases
cadmium uptake and depletes zinc,

a cadmium antagonist (Sharma 1991), was associated with hypertension in a study done in Japan (Watabayashi 1994). Blood lead has repeatedly been correlated with hypertension (Goyer 1993). Moreover blood lead levels are relatively elevated in neurologic impairments, osteoporosis, and renal cancer in epidemiologic studies. Even though compared to cadmium lead is not very toxic, lead met the Hill criteria used to prove causality based on the assumption that an increase in blood lead is caused by an increase in lead exposure (Goyer 1993).

Although there is wide agreement that lead is a major environmental pollutant, the basis of its toxicity is not certain. There are reasons to suspect that cadmium has something to do with lead toxicity. In a group of individuals with the same exposure to lead in the environment and food, the blood lead will be consistently higher in individuals with genetic susceptibility to toxic effects of cadmium, a poor diet, or increased levels of stresses of any kind. Unfortunately, blood cadmium levels do not necessarily correlate with blood lead (Berglund 1994) even though blood lead is indeed influenced by free cadmium ions. Cadmium induces zinc deficiency that increases lead uptake from the gastrointestinal (GI) tract increasing blood lead. Lead induces increased cadmium absorption from the GI tract, causing

cadmium-induced resorption of bone where lead is stored, increasing blood lead (StewartPinkham, 1989b).

By taking into consideration these metal interactions, one can see that *relative* increases in blood lead, that are statistically significant, could measure a toxic effect of cadmium rather than increased lead exposure. The well-researched linear relationship of blood lead with toxic effects could be due to the fact that blood lead is a *response* to the toxic effect, not the *cause* of the toxic effect. The very large epidemiological studies that have used blood lead levels as a correlate with toxic effects could in fact be used to understand the effects of free cadmium ions in humans and wild life. Because these possibilities are speculative they do not provide scientific proof.

Precautionary Principle. Fox

(199 1) 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 which will protect our ecosystem. He calls this "the precautionary principle." This paper uses his guidelines to assess cadmium exposure and toxicity. Data are taken from a wide cross strata of sources: algae, lichens, rats, beavers, trees, and humans, since all forms of living cells are affected by it. New information on how cadmium stresses cells, organs, and individuals

will be explored. Because of cadmium's unique ability to interact with inorganic and organic chemicals, and biological agents, these interactive effects will be presented. Health problems exhibited in one species will raise the possibility that the same or related health problems are occurring in other species, *including humans.* Multiple health and environmental effects will be considered. Finally, implications for public policy will be examined.

Sources:

The task of measuring cadmium air pollution is a daunting one. There are a myriad of sources. For instance, there are irregular releases of cadmium into air coming from

such natural sources as volcanoes and forest fires (Mislin 1987). An increase in cadmium air pollution accompanies population growth because cadmium air pollution is a natural product of burning coal, oil, wood, sewage sludge, and garbage. Industry, including steel, iron and non-iron metal production, cement and wood production and agriculture dependent on phosphate fertilizers, contribute to cadmium air pollution (Garty 1993).

Rapidly growing plants absorb cadmium from natural and human sources. Wind and high temperature move cadmium from plants into the air (Beauford 1977) in the summer. In the fall, the cying cells release

cadmium where it is trapped in the ice and snow in the winter. When snow melts in the spring, cadmium is released suddenly (Abrahams 1988), contributing to springtime increases of cadmium in food and animal tissues.

Cadmium air pollution is affected by lead air pollution. In this century lead pollution from leaded gasoline rose to a peak in 1970 and then fell back to its 1900 level. It is worth noting that lead can block cadmium uptake into plants, thus, blocking its passage back into the air (Djingova 1933). Hence, the recent global decrease in lead air pollution allows cadmium levels to climb even higher! The use of a great variety of chemicals in agriculture and industry has adversely affected global air, with recognized impacts in wildlife (Colborn 1992). The incineration of garbage has increased the release of hydrogen chloride, which reacts readily with cadmium compounds to produce cadmium chloride, a highly soluble compound which enters cells more readily than other salts (Oberdoerster 1992). As the ratio of lead and cadmium has changed dramatically over this century, the form of cadmium has changed to one even more readily taken up by cells and exposures are combined with other toxic organic compounds and metals.

Traps. Decreasing the harmful effects of cadmium air pollution on our globe are eco-systems that act as cadmium "traps." Wetlands are

beneficial cadmium traps, even though they also release cadmium back into the atmosphere. All forests act as traps to some degree since they moderate wind and high temperature. Forest fungi can accumulate up to 687ug/g cadmium dry weight (Wondraschek 1993). In rain forests, the majority of plants have very low levels of cadmium but the soil is highly contaminated, containing 6.9 ug/g in a mountain rain forest in Sri Lanka (Jayasekera 1993) compared to 0.1 ug/g in most agricultural soils. The rain forest acts as an excellent cadmium trap.

House dust is another trap for cadmium. It has harmful effects on humans by increasing their exposure to this pollutant. Mites, dander, and molds, which contribute to house dust, concentrate cadmium coming from all environmental sources, making indoor air higher in cadmium than outdoor air. House dust contains about 6-8 ug/g cadmium in non-smoking homes impacted by environmental cadmium air pollution (Stewart- Pin kha m 1991c).

Cigarettes. In humans, the most important source of cadmium exposure is active and passive cigarette smoke (Sharma 1983). The cadmium in tobacco plants varies with soil pH, and cadmium pollution in soil, water, and air. It averages 1.48ug/g in most cigarettes but

attains a level of 8.6 ug/g cadmium in polluted areas in China (Yue 1992). Indoor air cadmium is highly correlated with environmental tobacco smoke concentration (Sung 1991). The sidestream smoke which comes from the burning tip has 5 times as much cadmium as the mainstream smoke which is directly inhaled. It also has five times as much cadmium as lead. 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). See Figure below.

Exposure:

Problems. Detecting exposure to cadmium from cigarette smoke is easy: the concentration of cadmium in blood is associated with urinary cotinine levels, an index of active smoking and environmental tobacco smoke exposure in adults and children (Willers, 1992). Detecting exposure to environmental cadmium is more difficult. One of the first problems in assessing cadmium air pollution is to determine the extent of exposure. Quartz filters, which are still used to collect cadmium samples in air, no longer trap cadmium efficiently, because particulates, which formerly absorbed atmospheric cadmium so that it could be measured in standard air filters, have fallen dramatically with the decline in use of leaded gasoline.

Since cadmium is uniquely able to enter living cells at very low dose, it is essential to use plants and animals as monitors of pollution. To test the change in air pollution in the Netherlands, Sloof (1991) used lichens and found that the only metal increasing in air from 1982 to 1987 was cadmium and that it was coming from long distance transport rather than from local sources of contamination. Levels of cadmium are not constant. Higher levels are found in soil and plants at higher elevation and on western slopes that receive more precipitation (Heinerich 1993).

Use of Genes and Gene Products. To measure environmental and human exposure to

cadmium air pollution, a new way of measuring cadmium air pollution has now emerged from molecular biology. This method involves the detection in plants and animals of genes and gene products that produce cadmium tolerance and which are induced with exposure to cadmium. In the unicellular marine algae Tholossiosirc weissflogii, free cadmium increases the synthesis of phytochelatin, a metal binding protein found in plants, at the very low threshold of less than 1×10^{-12} M concentration (Ahner 1994). A specific amplification and rearrangement of a gene for a metal binding protein appeared in bluegreen algae adapted to increasing cadmium levels (Gupta 1992). A cadmium resistance protein gene, rapidly induced with cadmium exposure in an earthworm, is a possible candidate for biomonitoring cadmium input on land (Willuhn 1994). In the Netherlands, which we know from lichens is being exposed to increasing cadmium air pollution, all roundworms studied were tolerant to cadmium (Kammengo 1994). Apparently, the detection of genes and gene products that produce cadmium tolerance provides a reasonable index of environmental cadmium exposure.

In animals, including humans, the organ that contains by far the most cadmium is the kidney. Kidney cadmium levels are influenced by factors other than air pollution (Chan 1993). With overt kidney disease, cadmium-containing cells are sloughed into the urine, decreasing the levels in kidney cortex. Nevertheless, just as in plants and lower invertebrates, with cadmium exposure, kidney cells increase their production of metal-binding proteins called meta l lothioneins, causing large amounts of cadmium to be stored in the kidney. Thus, kidney levels of cadmium indicate exposure and tolerance.

A mutation that results in the

loss of a charged amino acid at the hinge between the metal binding domains makes the metal binding protein unable to bind cadmium (Cody 1993). Thus, with increasing exposure one could have persistently low levels of cadmium in the kidney tissue but the kidney could be suffering from toxic effects from free cadmium ions. Paradoxically, low levels of cadmium in kidneys with increased cadmium exposure indicate increased susceptibility to cadmium toxic effects.

Kidney levels. Kidney cadmium levels have been analyzed worldwide and can be used as a measure of global cadmium exposure. In a study from northwest Germany on deceased persons, individual cadmium values ranged 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 50. As expected, non-smokers from a polluted area had a significantly higher level of cadmium than non-smokers of the same age from an unpolluted area (Hahn 1987). At all ages there were low values, indicating increased susceptibility since by lichen studies there is increased exposure. See Figure below.

In Japan, where the kidney cadmium levels have been the highest in the world, mean cadmium levels have increased from 43.95 to 73.47 ug/g in the past decade in spite of a drop in cadmium levels in food supplies (Noda 1993). As far away as Antarctica, penguins at the south polar cap have cadmium levels ranging from 5 to 160 ug/g (Elinder 1992), attributed to their diet of krill. Krill absorb cadmium from the water, which in turn receives cadmium from air pollution.

On the other side of the world, cadmium levels in the kidneys of caribou from the Canadian Yukon, Northwest Territories, northern Quebec and Norway have measured up to 166 ug/g in a 15 year old animal (Gamberg 1994). High levels of cadmium also were found in the kidneys of red deer from the De Veluw area of the Netherlands (Wolkers 1994). From these widely varied samples, one can conclude that global cadmium air pollution, interacting with locally different levels of cadmium in background soil and local bodies of water polluted by agriculture and industry, has exposed animals, including humans, inducing high levels of metal-binding proteins in the kidneys of some individuals.

Hair Levels. Since kidney

samples are not generally available in living subjects, alternative measures of exposure are necessary. Hair is easily obtained and can be analyzed for multiple elements including cadmium content (Stewart- Pin kha m 1989). Using this measurement, hair cadmium in children is well correlated with cadmium air pollution (Prucha 1987). One survey showed that hair cadmium in newborns of nonsmoking mothers was significantly influenced by exposure to a local copper smelter which was polluting the air with 1 ton of cadmium per year (Lagerkvist 1992).

In another striking example, the hair of beavers moved to the Biesbosch, an estuary in the Netherlands contaminated with cadmium coming from the Rhine and the Meuse, increased three-fold three years after release. The average cadmium content of their food source was 6.9 ug/g (Nolet 1994). The cadmium concentration in the kidneys and hair of the beavers correlated with that of the tree bark they fed on. The mean cadmium kidney concentration more than doubled (24 to 55 ug/g). Bark, kidney, and hair cadmium levels in this study were influenced by cadmium air pollution which was shown in a lichen study to be increasing in air (Sloof 1991).

Standard Deviation. The standard deviation (SD) of hair cadmium was very high in beavers which were moved from a setting of

low contamination to high contamination; this was also true of the SD of kidney cadmium. In animals which were tolerant of a high cadmium exposure and were in a steady-state exposure, the hair and kidney cadmium levels were high but the SD was low. The numbers of beaver studied were small but the SD of kidney cadmium in northwest Germany was also very high, a region exposed to increasing levels of cadmium air pollution. A high SD in either hair or kidney cadmium appears to indicate increasing exposure. See Figure below.

The conclusion drawn from these data are sobering: the high SD for cadmium measured in kidneys around the world implies a *global* increase in cadmium exposure, matching the estimated increase coming from multiple sources around the globe.

Cellular Stress Responses:

In contrast to other toxic metals of concern like lead and mercury, cadmium is actively taken up by new cells with fluid membranes and transported within plants and animals to distant sites where it readily affects cells of multiple organs, producing a great number of effects (Friberg, 1971, Webb 1979, Foulkes 1986, Nordberg 1992). Cadmium affects multiple ion channels (Schoenmakers 1992). It triggers cytotoxic actions by disrupting ionic balances across membranes (Koizumi 1994a). In conditions of acidosis, which cadmium

exposure can induce, it is very toxic to mitochondria, while it is without effect at a neutral pH of 7.4 (Koizumi 1994b). The cellular effects of cadmium are strongly influenced by other metal ions, especially calcium, zinc, magesium and lithium. Lithium, for example, by promoting alkalinization of the intracellular space (Munsch 1994), may antagonize a toxic effect of cadmium on cells triggered by acidosis.

Stress Response. Although cadmium has been considered a purely toxic metal ion with no essential function, it appears to have been harnessed by the cell to play an essential role in the stress response. There is a chain of evidence that supports the hypothesis that cadmium is a key mediator of the stress response through the signal transduction pathway linking cell surface effects to nuclear effects on genes, influencing cell proliferation, cell

death, mutagenesis, carcinogenesis, and inflammation.

At the molecular level, there appears to be a cadmium-sensitive cell receptor that interfaces with viral proteins, cancer proteins, and compounds associated with inflammation (Smith 1989). Certain metal ions (zinc>copper>lead) can block this receptor. Cadmium activation can produce hormone-like signals which increase free calcium, stimulating many effects. In addition, 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. Moreover, by moving into the nucleus and activating gene transcription, cadmium, like calcium, acts as a second messenger, producing stress proteins and turning off the normal housekeeping genes (Smith 1994). The effect on gene expression is seen in experimental studies with cadmium, where multiple enzymatic changes were observed when no morphologic effects were found (Wloch 1992b).

The process of signal transduction is a complex one with many intermediate events. Increased intracellular calcium is one key event (Ghosh 1995). Cadmium has 1,000 times more affinity than calcium for an enzyme which pumps calcium out of the cell (Verbost 1989). Free intracellular cadmium increases intracellular

calcium, an important second messenger.

Metallothioneins (MT), which we noted earlier are induced by cadmium, are also induced by zinc. One promotor for MT responds only to zinc and another responds to either cadmium or a glucocorticoid, a steroid hormone released from the adrenal gland with stress, (Takeda 1994).

Cadmium has 40 times more affinity than zinc for the DNA zinc finger binding site for the glucocorticoid receptor (Freedman 1988). In stress situations, serum zinc levels are low, enhancing the effects of free cadmium ions.

Cell proliferation. The threshold for its stimulating effect on cell proliferation is 1 X 10^{-0} M (von Zglincki 1992) but in normal appearing cadmium 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 cadmium exposure are bidirectional.

Cell Death. The mineral balance, rather than dose alone, dramatically influences effects. There is a calcium and zinc containing enzyme that is a critical step in apoptosis, programmed cell death, in which cells die without stimulating inflammation (Lohmann 1993). Cadmium can take the place of calcium and stimulate apoptosis or take the place of zinc and block apoptosis. Generally, zinc protects the cell from cadmium cytotoxic

effects, but sometimes a cytotoxic effect is helpful. With high doses of cadmium causing zinc deficiency, cadmium appears to exert a cytotoxic effect on spontaneous and chemically induced cancers in mice (Waalkes 1991), thus functioning as an anti-carcinogen.

Mutagenesis & Carcinogenesis. Cadmium is directly toxic to DNA (Littlefield 1994) and results in frame shift mutations (Heckman 1992). In the presence of magnesium and zinc deficiency it interfere with DNA repair (Nocentini 1987, Littlefield 1994). When combined with other metals like nickel, chromium and cobalt and a variety of organic chemicals contaminating the environment, cadmium potentiates toxic effects leading to multiple organ damage, mutagenesis and carcinogenesis. Since exposures are mixed, effects are the result of interactions, but the level of free cadmium is an indispensable factor. Co-exposure of low dose cadmium 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 cadmium did, they potentiated the tumorigenic effects of low dose cadmium (Tehseen 1992, Schaeffer 1991).

Inflammation. Both zinc and magnesium antagonize cadmium's pro-inflammatory effects. 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 cadmium receptor, this enzyme disappears from the surface, effectively increasing inflammatory signals (Shipp 1991). Intracellular magnesium deficiency increases free cytosolic cadmium ions (Quamme 1992). Magnesium deficiency in rats leads to an early peak in substance P, which in turn stimulates chemical mediators of inflammation (Weglicki 1991).

Cadmium activates cyclooxygenase releasing prostaglandin E2 (PGE2) which plays a role in bone resorption (Miyahara 1992). Prostaglandins are biological mediators linked to inflammation and immunity with helpful and harmful effects. Interleukin-1, a cytokine secreted by immune cells (O'Connell 1994) is indirectly stimulated by cadmium. Oxidative stress, acidosis, decreased mitochondria) function, and a myriad of stress responses, including elevated intracellular calcium, and release of interleukin 1 and prostaglandin E2 are some of the cellular effects arising from free cadmium ions.

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 cadmium resistance they can persist and cause disease.

If cadmium induces DNA damage in a setting of magnesium and zinc deficiency, preventing DNA repair, the cell is permanently damaged in ways that can lead to cancer or degenerative changes. Thus, cadmium can be both beneficial and detrimental at a cellular level alone and in combination with a great many other metal ions and organic chemicals of concern. Global cadmium air pollution affects cells by influencing, in an unpredictable way, the level of free cadmium ions, a highly toxic metal and a potent mediator of stress responses.

Organ Stress

Although in the past, the kidney was considered the target of cadmium toxicity, all organs are affected by cadmium and blood vessels are particularly reactive. Oxidative stress occurred in all tissues tested in animals exposed to 25 and 500 ug cadmium /kg (Manca 1991). Lungs and brain were the most responsive. The lungs showed an increasing effect with increased dose but in the brain the low dose effect was equivlent to the high dose effect. The oxidative stress measured by the amount of TBARS in the tissues following cadmium exposure by intraperitoneal injection was not at all correlated with the level of cadmium picked up by the tissue. Although some effects were very transient, appearing in 2-6 hours but gone by 72 hours, in the lung

and brain the effects were persistent. See Figure below.

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).

Brain. The brain is very vulnerable to toxic effects of cadmium because brain metallothionein is not able to bind cadmium. The blood brain barrier protects the brain from cadmium exposure. During fetal development the placenta has this barrier function. Unfortunately, exposure to paternal smoke doubles the risk for anencephalus and spina bifida (thong 1992) in newborns. Low dose cadmium exposure in pregnancy changes multiple neurotransmitters

in rat pups (Rajenna 1990). Low dose oral lead increases cadmium levels in the brain 10 fold (Lockett 1986). Manca showed that cadmium exposure increased lipid peroxidation in the brain without increasing measurable amounts of cadmium in the brain. There are three possible explanations for this data: 1) the level of uptake was below the detection limit, 2) a toxic effect on brain blood vessels caused the effect or 3) chemicals increased in the blood with cadmium exposure crossed into the brain causing the effects. Heat shock proteins induced by maternal cadmium exposure affect neuroepithelial cells in mouse embryos causing malformations (Honda 1991).

Lung. Cadmium exposure can protect the lung from influenza (Chaumard 1991), oxygen toxicity, and radiation damage (Salovsky 1993). When cadmium is instilled into one lung it causes destruction and fibrosis while stimulating normal growth of the contralateral lung (Frankel 1991). As cadmium produces injury it stimulates adaptive changes as well.

Liver, Kidney and Heart. When cadmium is instilled in the trachea of rats, acute phase response proteins are induced in the liver of the animal (Frankel 1991). In a rat study, chronic administration of cadmium caused kidney, liver, and heart damage with prominant atherosclerotic effects on blood velssels (Schroeder 1964). A dosage of an organophosphorus

compound and cadmium, that induce minor changes when given separately, together damage the liver and kidney in 24 hours (Chishti 1993)

Bone. Cadmium decreases the mechanical strength of bone. Feeding cadmium 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 cadmium 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).

Endocrine System. Cadmium has complex hormonal effects mediated by its effects on endocrine organs. It activates the hypothalamic adrenal axis (Hidalgo 1987). It

stimulates the pituitary ACTH cells while inactivating the gonadotropin- and thyrotropinsecreting cells in the catfish (Jadhao 1994). Thyroid deficiencies and disturbances in fertility can be expected from such effects.

Dehydroeplandrosterone (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. Cadmium could possibly act on the adrenal to cause its decline, directly or possibly through

depleting the adrenal of lithium. The two organs with the most lithium are the pituitary and the adrenal (Lehmann 1994), both targets of cadmium toxicity. Supplemental nutritional lithium has effects similar to those produced by DHEA (Schrauzer 1994).

Aging. The consequences of chronic stress at an organ level are multiple mineral and glandular deficiencies associated with premature aging. Magnesium deficiency, which greatly increases the toxic effect of free Cd (Quamme 1992), is thought to cause immunosuppression, muscle atrophy, central obesity, osteoporosis, hyperglycemia, hyperlipidemia, and atherosclerosis (Durlach 1993). Zinc deficiency, a cadmium toxic effect, also causes many problems associated with aging (Bin 1994) including hypertension (Schroeder 1975), birth defects (Hartsfield 1992), and carcinogeneisis (Oldiges 1989). By inducing chronic organ stress, cadmium depletes minerals and glandular substances associated with aging, accentuating its toxic effects.

Individual Stress.

Of all the physical, chemical and biological stimuli that trigger the stress response, including pH, temperature, radiation, and trauma, the most potent are emotional stresses (Hidalgo 1987). Thus it is at the individual level that the effects of cadmium need to be addressed.

Psychological effects are linked to neurological, endocrine, and immune effects. Global cadmium air pollution affects the response of individuals to all stressful stimuli, especially emotional stress.

Life Style. In humans life style choices regarding smoking, alcohol, and drug use, diet, sun exposure, exercise, and other activitities and beliefs that affect emotional stresses influence an individual's exposure, uptake, and toxicity of free cadmium in conjunction unction with other metals and organic chemicals. If the DNA is not altered, exposure can result in increased hardiness and complete healing. If, on the other hand germ cells are damaged, the off-spring are negatively affected or not viable. If cells in organs are damaged, different effects occur depending

on where the damage occurs. A cadmium induced frame-shift mutation in a gene for an enzyme involved with drug and carcinogen metabolism in the liver alters cancer susceptibility and affects the metabolism of 30 therapeutic drugs, including beta blockers and tricyclic antidepressants (Smith 1992).

Nutritional status is extremely important in modulating the response. With increased dietary cadmium there is decreased zinc absorption (Coppen-Jaeger 1989). Cocoa is the beverage which contains the most cadmium and also significant quantities of nickel (Pedersen 1994), decreasing zinc

absorption. Allergic patients are more sensitive to cadmium because immune activation results in urinary losses of zinc (Melichar 1994). Catecholamines, chronic stress, caffeine and other psychostimulants increase magnesium excretion in the urine. Insufficient stomach acid decreases the absorption of both magnesium and zinc. Areas with high calcium and low magesium in soil and water can lead to tissue magnesium depletion. Multiple conditions can therefore make a plant or animal more susceptible to effects of cadmium air pollution.

Substance Abuse. Cigarette smoke is a major source of exposure to cadmium and multiple metals and toxic organic compounds. Emotional stress often triggers use of cigarettes. With the decline in leaded gasoline usage, cigarettes no longer contain lead making them even more toxic since the mid 80's. Cigarette smoking increases the risk of alcohol abuse. Alcohol consumption increases cadmium uptake from the GI tract and accumulation in tissues (Sharma 1992). By increasing free cadmium ions in cells, alcohol enhances the effects of cadmium, reflected in oxidative damage (Sharma 1991,1992). See Figure below.

Alcohol alters the red blood cell membrane in a manner that increases lithium (Adebayo 1994), zinc, and magnesium losses in the urine, enhancing sensitivity to cadmium. Cadmium

exposure makes rats prefer alcohol to water (Nation 1987), suggesting it also increases the risk of alcohol abuse in humans.

Lithium deficiency, which can be aggravated by cadmium-induced increases in aldosterone (Strazzullo 1994,Webb 1977), is associated with narcotic use and multiple mental health problems including suicide, homocide, and other violent crime (Schrauzer 1991). Low levels of lithium and cobalt (from B-12) in scalp hair (Schrauzer 1992) are associated with violence in humans. 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).

Substance abuse results in increased exposure and toxicity from cadmium, which directly and indirectly can influence these diverse problems. Moreover, teenagers and young adults put at risk their unborn children by experimenting with drugs and

alcohol even if they quit prior to conception.

Food. Countering this toxicity is the nutritive value of food. Cadmium in human food is very well absorbed compared to cadmium in rat chow (Anderson 1992). This difference has been linked to fiber in the diet and fiber strongly influences bacteria! flora. A nutrient dense, high-fiber, plant-food diet with adequate protein and fish oils is the most protective against experimental cadmium 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, StewartPinkham 1991 b). Also, herbs and spices that are used in various cultures as medicinals or flavorings counter toxic effects of cadmium.

Cadmium, 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 cadmium, 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 1991).

Gene differences. Although with adaptation free cadmium ions can be bound, turning off the stress signals, mutations in gene products cause persistent sensitivity to its toxic effects. Mutation in the gene for

metallothionein blocks its ability to bind cadmium but other mutations have this effect as well. The gene for the chloride channel is very similar to the gene for cadmium resistance in yeast.

The mutations in this gene that result in cystic fibrosis in humans cause a loss of cadmium tolerance in yeast. The gene for cadmium resistance in yeast is also very similar to the gene for multiple drug resistance protein (Szczypka 1994). This gene is found in cancers resistant to chemotherapy. Inducing cadmium tolerance in cancers can have a negative impact on human health. It is possible that many diseases will be found to be caused by cadmium-induced gene amplifications or cadmium-induced mutations that decrease or increase cadmium tolerance of specific cells.

With our current highly processed diet, devoid of essential nutrients and adulterated with pesticides and other chemicals, individuals exposed to cadmium air pollution and environmental toxic chemicals or cigarette smoke are vulnerable. Cadmium exposure can enhance an individual's susceptibility to disease without changing fetal weight or birthweight (HazelhoffRoelfzema 1987). With its direct toxicity and immune suppressive effects it is likely to promote disease outbreaks in an unpredictable manner (Sovenyi 1993). The ability of multiple minerals to act synergistically or antagonistically in the stress response makes it

impossible to determine the effect of cadmium on an individual based on the dose of cadmium. It's effects on individuals at low dose are influenced by many factors: age, gender, species, genetic factors, *prior* nutritional history and exposure to cadmium and other stressors, and *current* nutritional history and exposure to toxic metals, organic compounds, and biological pathogens. These interactions will be addressed in the next sections.

Inorganic Chemical Interactions:

Problems. Although free cadmium metal ions have potent effects on all aspects of cell function, unbalanced inputs of other metal ions strongly affect the levels of free cadmium ions in the cell and on the cell membrane receptor. Unraveling the multiple, complex, and seemingly contradictory interactions between cadmium and other minerals is essential, but as with exposure measurements, there are inherent uncertainties and complexities. First, there are so many interactions with other metal ions (Blazka 1992). Second, toxic metals can enhance cadmium absorption, producing effects from cadmium at levels that elude conventional measurements of cadmium because the threshold for effects, 10^{-12} M, is much lower than the threshold for analysis,

which is generally 10^{-}' M. Using a new fluorescence detection

of cad mium-8-hydroxyq u1noline developed by Hamada (1994) it may be possibly to detect cytoplasmic and nuclear cadmium at $_1{}^X 10^{-12}$g/cell, clarifying these issues.

Lead. Lead is a key factor in cadmium air pollution. In a study of cadmium levels in heartwood of the oak, cadmium levels declined during the period of increasing lead pollution from 1947 to 1970, even though cadmium sources of pollution were not declining. After 1970 cadmium levels rose abruptly (Hagemeyer 1993). By blocking cadmium uptake into plants, lead blocks its ability to move back into air. Lead is a kind of cadmium trap. Many other studies examining plants exposed to varying levels of lead. show the same effect: in the areas closest to the source with the highest lead concentrations plants exhibited a lower uptake of cadmium than areas farther away having less exposure to lead (Hertzig 1993).

Harmful Effects. Although atmospheric lead pollution blocks cadmium uptake into plants, lead ingestion *increases* cadmium uptake in the brain by breaking down the blood brain barrier (Lockett 1986, Burger 1990, Shuckla 1987). When researchers gave lead to animals, they assumed the neurotoxic effects they produced were due to lead. In only the 3 mentioned studies did scientists investigate effects of lead ingestion on cadmium absorption and uptake into the brain. Lead

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ingestion coming from leaded gasoline use increases cadmium uptake into the brain where it has highly toxic effects (Stewart-Pinkham 1989b).

Research has shown that low dietary intake of iron and calcium and exposure to cigarette smoke increases cadmium absorption (Kowa) 1988), conditions also associated with increased blood lead (toyer 1990, Rooney 1994). Blood lead has been assumed to be a marker of exposure to lead when, in actuality, it serves as a marker of cadmium absorption, as well.

Beneficial Effects. In equimolar doses, the two metals can mutually cancel each other's individual effects (Nation 1989). At a biochemical level, lead can block cadmium effects on the cadmium cell surface receptor. Combined exposures significantly lower lead and cadmium concentrations in liver and kidneys of rats (Skoczynska 1994). The striking increase in longevity of the cohort of individuals who reached middle age during the time of leaded gasoline pollution might be due to this antagonism.

For instance, animals exposed to endotoxin, a glucocorticoid, and lead all survived, while when exposed to these conditions together with cadmium they all died (Cook 1974). It appears that in stress situations, simulated by the glucocorticoid administration, a low dose of lead may have a *beneficial* effect by modulating the stress

response controlled by this cadmium receptor. Other indications of a beneficial effect from lead come from feeding experiments (Schroeder 1964) in which a low dose of lead fed to mice and rats resulted in less metastatic disease and decreased liver, kidney, and heart disease in males and females and increased longevity in females. See Figure.

Ingestion of red wine, which has ten times more lead than other beverages (Pedersen 1994), is associated with decreased cardiovascular disease in France. Although its lead content has not been thought protective, the findings in Schroeder's study raises this possibility.

Other Toxic Metals. Cobalt, nickel, iron, and manganese can all stimulate the cadmium cell surface receptor and therefore can be expected to have synergistically toxic effects with cadmium. Cadmium, cobalt, and nickel produce similar malformations in the frog, suggesting they could be acting through the same mechanism (Plowman 1994). This study was done in Connecticut

which is exposed to cadmium air pollution coming from waste Incinerators. It is possible that cadmium exposure coming from ambient levels in air could be acting with the intentionally added nickel and cobalt. Cadmium and nickel are highly synergistic (Murthy 1991), but cadmium is more toxic to DNA. In a model system using murine sarcoma virus, nickel produced a splicing defect mutation while cadmium and chromium produced frameshift mutations (Chiocca 1989). Deletions of up to 300 nucleotides were noted with Cd exposure in this system (Heckman 1992). Cadmium, chromium, and nickel all inhibit DNA repair in mammalian cells and are co-mutagens with ultraviolet rays (Hartwig 1989) and are elevated in patients with lung and coloectal cancer (Martin Mateo 1990).

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

It is quite possible that many

studies involving metals may have a hidden effect through a change in ambient cadmium uptake, since it has such a very low threshold for effects and can enter the cell through multiple channels. We have seen that lead ingestion can increase cadmium uptake into the brain. Aluminum, also, increases cadmium absorption (Sugawara 1993) and increases tumors in males (Schroeder 1975), although very little of it is absorbed. It is reasonable to hypothesize that cadmium absorption caused by aluminum ingestion increased the tumors. Using new techniques to analyze cadmium in cells, these possibilities could be explored.

Organic Chemical Interactions:

Environmental Toxic Organics. Cadmium 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 cadmium chloride with [3H]benzo[cjpyrene injected into the arterial circulation of rat lungs, cadmium alone significantly affected its metabolism (Williams 1984). So, although these other metals can substitute for cadmium at the cell surface receptor, they do not influence the metabolism of chemicals the way cadmium does.

the animals transferred were found dead of disease, suggesting that they were experiencing toxic effects in their new environment. They had not developed cadmium tolerance. Beavers from a polluted area in Germany, averaging 467 ug/g cadmium 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 cadmium.

There are several reasons why cadmium could be expected to be the cause of the reproductive failure in the beavers moved to the contaminated site. In a contiguous area in northwest Germany, rabbits are experiencing reproductive failure, associated with elevated cadmium in their gonads (Lutz 1993). Further, cadmium air pollution could affect reproduction by depleting lithium (Anke 1991), a possibility which could be checked by analyzing hair or adrenals for lithium. The olfactory bulb of the animals can be affected by breathing cadmium air pollution through a direct nasal exposure (Evans 1992). Inability to smell could affect sexual behavior without even affecting gonadal cadmium levels. Erectile dysfunction was found to be the lowest dose effect of cadmium on rats (Clark 1994).

The findings of reproductive failure, disease, and decreased life span in animals exposed to

increasing levels of cadmium in the Netherlands suggest that increasing exposure to cadmium air pollution could have a detrimental effect in humans, animals and plants that are not adapted to cadmium or genetically cannot tolerate increased exposures. Because these impacts are of such potential importance, follow up studies are urgently needed. At the present, there is suggestive evidence that through effects on biological systems cadmium can contribute to global warming, increase the virulence of disease, and produce disabling effects in vulnerable individuals, including reproductive failure.

Conclusions:

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

Human population growth and destruction of forests have increased environmental cadmium exposure. Cigarette smoke contributes heavily to cadmium exposure in humans.

Genes and gene products producing cadmium tolerance in cells respond to cadmium exposure in a dose response manner. Many factors modify this gene expression creating a high SD in hair and kidney cadmium levels in groups of individuals exposed to increasing cadmium exposure.

1. Plants and animals appear to use

1.

the Human Environment: Toxicity and Carcinogenicity. Lyon:IARC Sci Publ (118), 1992

Obordorster G. Pulmonary deposition, clearance and effects of inhaled soluble and insoluble cadmium compounds. IARC Sci PUN 1992(118):189-204

O'Connell NA. Kumar A Chatzipanteli K. et a1. Interleukin-1 regulator corticosterone secretion from the rat adrenal gland through a and prostaglandin E2-independent mechanism. Endoerinology 1994:135:460-7

Oldgies 11. Hochrainer D. Glaser L[t]. Preliminary results from long- term inhalation study with cadmium compounds. Environ Chem 1959:23:3?

Oner G. Izgut-Uysal VN. Senturk UK. Role of lipid peroxidation in cadmium-induced impairment of the gastric mucosal barrier. Food & Chem Toxicol 1994:32:799-804

Ozonoff D. Colten ME. Cripples A, et al. Health problems reported by residents of a neighborhood contaminated b[y] a hazardous water facility. Amer J Industr Med 1987:1 1:531-97

Pedersen GA. Mortensen GK. Larsen Ell. Beverages as a sourc[e] of toxic trace clement intake. Food Additives Contaminants 1994;11:351-363 113SI-363

Plowman NIC. (31-1)ac-lv~irikoviC S. NLUrill I Il0l)I'01_ S.M. S111)dLnn:11 FW Ji. Alalfirtnations persist alrcr metamorphosis of XeiiopLis Iltcvis tadpoles exposed to Nit r. Cot . or C'd2 ill FE'l'A_X assa[y]s. -1'erzitot;eiiesis. Caciiio-eiiei,. K, \ILltllgOnWSis 1994:14:135-144

Pool-Zobel BL, Letzmann N, Knoll M, et al. Detection of genotoxic effects in human gastric and nasal mucoso cells isolated from biopsy samples. Environ Mot Mutagenesis 1994;24:23-45

Prucha J. Heavy metal content of children's hair. Zentralb Bakferial Mykrobiol Hyg 1987;185:273-290

Quor-nme GA. Free cadmium activity in renal epithelial cells is enhanced by rAg2+ depletion. Kidney Int 1992;41:1237-1244

Rajanna. B., Hobson. XL. Bo[y]kin. \I., and Chem, C.S.: Fllects oh chronic treatment with CZ1,1filitlnl oil XFPases. uptake of catecholantines. and lipid peroxidation in rat brain syrlaptosonics. Ecotoxicol l'miron Safety 20:36-41. 1990.

Raraz AG. Biological and biotechnological waste management in materials processing. J of Metals 1995: Februar[y]: 56-63

Reese AC, James IR, Landau LI, Lesouef PN. Relationship between urinary cotinine level and diagnosis in children admitted to hospital. Am Rev Respir Dis 1992;146:66-70

Reiss RA, Haas CE, Karki SD, Gumbiner B, Welle SL, Carson SW. Lithium pharmocokinetics in the obese. Clinical Pharnictcology and Therapeutics 1994;55:392-398

Rodriguez-Arita A, Dorado G, Navas J1, Pueyo C, LopezBarea J. Promutagen activation by fish liver as a biomarker of littoral pollution. Environ Mol Mutagenesis 1994;24:116-123

Rooney BL, Hayes EB, Allen BK, Strutt PJ. Development of a screening tool for prediction of children at risk for lead exposure in a midwestein clinical setting. Pediatrics 1994;93:183-187

Sacco-Gibson N. Cliatidlin S. Brock A. SicIklc, AR. Patel 13.
1legSIZILI R. Johnston S. Peterson 1), 1 111AILICILJI-N" Na\I. Cadmium effects on hone resorption in o\aricclorllizeCl. aged 1)0a00s. 'I'Oxicol Appl Plmriitacol 1992;1 13(2):274-283

Sokoto S. 1\cami l 11rioki Y Kozuki IL Shimizu S, NIMS·Lida N4, Morkarlia 'I". Effects of cadmium on i[ll] vitro and ill vivo en thropoiesisxrvthruid progenitor cells(CFU-E), iron, and ei\iluo[l])oietin i[ll] cadmium induced iron deficiency ammiia. Experiment licinatol 1988:16:581-587

Salovsky P. Shopova V. Daliclina V. Nlzire\ R. Pandurska A. Enhancement ol'tho piekiinotoxic cll'oct oi'cadilliUlll acelato by ionizing radiation [ill] the rat. Environ llcaltll 1993i101 suppl 2:269.274

Se Sena DK. \ILlld1.\ DC. Chandra SV. I'iiiiii-„'otoxic and tel-atogeiiic cll'm.s ol'iiiteiactiorrs ol'cadinitini and lindano [ill] rats. ACW I'lMI-IM11:01 'I'ONiL:1)ll 98MS[I]A 7?478

Schaeffer D.), '1'dlsooll WNI. Johnson I.R. McLaughlin GL. Hassan AS. Rcv'iioIds IiA. llatisei) I.G. Cocarcinogenesis 1),'meeji cadmium and Al_0610[_ 1254 i[ll] planarians is enhanced b[y] inhibition [ofgflitafl)ione] s\wliesis. Quality :A>suranre 199 1 : 1:31-41

Schoenmakers TJ, Klaren PH, Flik G, Lock RA, Pang PK, Bongo SE. Actions of cadmium on basolaeral plasma membrane proteins involved in calcium uptake by fish intestine. J Mem Biol 1992;127:161-172

Schrauzer GN, de Vroey E. Effects of nutritional lithium supplementation on mood. Biol Trace Ele Res 1994;40:89-101

Schrauzer GN, Shrestha KP. Lithium in drinking water and the incidences of crimes, suicides, and arrests related to drug addictions. In Lithium in Biology And Medicine, GN Schrauzer and K-F Klippel leas). VCH: New York, 1991

SeTij:ilizci (;N_ Shrestha U. Flores-:Arco Nil. Lithium in scalp hair oi 0 l l l t C r i m i n a l s . B i o l '(r a c e E l e 1 Res 1992i3-4:161-176

Schroeder ll-V Vinton \V'11. 13aklssZl ·I·I. Effects ol'cllrolllliulll. Cadmium and other trace metals oil growth aiidsur\ ival LWIlli:0. J Null- 1963.80.39-47

Schroeder HA, Balasso JJ, Vinton WH. The effects of lead, cadmium and chromium on rats. J Nutr 1964;86:51-57

Schroeder HA, Buckman J. Cadmium hypertension. Its reversal in i ats by a zinc chelate. Arch Environ Health 1967;14:693-7

Schroeder HA, Mitchner M. Life-term studies in rats: effects of aluminum, barium, beryllium, and tungsten. J Nutr 1975;105:421-7

Shoham J, Rosenboim J, Ophira D, Mil<ullsky Y, Jucha E, Ribak J. The correlation between blood and urine levels of cadmium and nasal and paranasal sinuses disorders. Internet Arch Occupat and Environ Health 1993;65(1 suppl):S91-93

Sharma G, Ha[l]h R, Gill KD. Effect of ethanol on cadmium-induced lipid peroxidation and antioxidant enzymes in rat liver. Biochem Pharmacol 1991;42 Suppl:S9-16

Sharma G, Nath R, Gill KD. Effects of ethanol on the distribution between the cadmium metalloih[l]onein and non metallothionein bound cadmium pools in cadmium exposed rats. Toxicology 1992,72:251-263

Sharma G, Sandhir R, Ncth R, Gill K. Effect of ethanol on cadmium uptake and metabolism of zinc and copper in rats exposed to cadmium. J Nutr

Verbost PNI, Ffik (I. Pan, PK. Q1 al. Cadmium inhibition ol'111c et-N-throcyte Cm2 - pump. A molecular inlcrproialioii. J Biel Client 1989:264:5613-s61

Vivoli G, Bergomi M, 1301'ClIZI 1'. UMltLI/.-AG. C',ISClgLa11di F, Cadmium [ill] blood. urine. and hair related to human Inti,crictision. .1 Trace Elcm Flectrol%Ie, llc:,Itll D1, 19893:139-14~

von Zglinicki T, Edwall C, Ostlund E, Lind B, Nordberg *M,* Ringertz NR, Wroblewski J. Very low cadmium concentrations stimulate DNA synthesis and cell growth. J Cell Sci 1992:103:(Pt 4):1073-1081

Waalkes IMP, Diwan BA. Weglioist CM. RIT-L! RM, Ward J\L Rice JM. Anticircirlogerlic ellects of cadmium i,13(,C31:1 IIIOLISO liver and lung. TOXICO1 A,1,11 PIWI IIIaCOI 1991 a: 110(2):327-33 5

Wade GC, Mandel R, Ryser H J-P. Marked synergism of dimethylnitrosamine carcinogens in rats exposed to cadmium. Cancer Res 1987;24:6606-6613

Wakabayashi K, Nakamura K, Kono S, Shichi K, imanishi K. Alcohol consumption and blood pressure. An extended study of self-defense officials in Japan. Inter J Epidemiol 1994,23:307-31 1

Webb NI, ed. Chemistr[y], HiodmiiiStIN. and of,c%IdiIIIIIIII, Anistcr&ini: Elsevier 'North Hollandflex,. 1979

Webber MNI. Selenium prevents the ,ro\\ I [I] I stimulatory 0 1 lects of cadmium oil human IWOSLI11C el)itbCIiL1]II. HiOdleill Bioi)li * \s Res Collin) 19[1],[5]: 127(3):87 1 -X77

Weglicki W13, Pliillips'I'M, J'atbobioloj \ ofnmni SiLIT i L~ , Q 11 &11.[c] :[] acylolkine"nourogenicA111.1 PIIvsiol 1992:263(3 I[i] 2):IZ734-737

Willers S. Atic\wll R. Rell1-0 1, Schutz Skmjimq G. Vzilitei M. Exposure to environmental tobacco smoke [ill] the household and urinar[y] cotinine excretion. heavy metal retention.andlung 1111101011.Arch 111610111 lcZ111111 992AT3i7-363

Williams SJ, Km-is MA. Menzel DR, Intetaction., of'bem' metals with the PH 1111101IMN metabolism of'131111-Icrizolzil)Nrelle. Environ Res 198434:212-226

Willuhn J, Schmitt-Wrede HP, Greven H, Wunderlich F. cDNA cloning of a cadmium-inducible mRNA encoding a novel cysteine-rich, nonmetallothionein 25 kDa protein in an enchytraeid earthworm. J Biol Chem 1994, 269t40): 24688-91

Wloch S. D'namics of 11101-Pbologiczll and L' in \todleilicA cll~lll-cs i the Placenta kfllomrl~; cadmiumintoxication_ Ginekol Pot 19921):(63(6):265-274

Wolkers H. \\'cn.siiigT, Groot BlUilldClillk G\\'. [1] 10u\N natal contamination in organs of red deer (Col \ LIS ek)I11IS) and wild ILI hoar (Sits scroFi) andthe effecton son[g] trace elcillorits. Science 01'111c Total Environment1994:144-191-199

Wondi-titscliek 1. Roder (!. X1011ilOrill" Ot'llcal) metals in higher fungi. It) Plants as Biomonitors, B. Markett ;ed). VCH: New York, 1993

Yamada 11. MiN'aIMM T. Sasaki)T. Inorganic cadmium increases the fi-C(111L!11C~ of chemically induced Chromosome aberrationsIII collared mammalian cells. Molar Res 1993302(3):137-4~

Yue L. Cadmium in tobacco. Biomedical Environ Sci 1992;5:53-56

Zhang J, Savitz DA, Schwingl PJ, Cal WW. A case control study of paternal smoking and birth defects. Int J Epidemiol 1992:21:273-278

Polluted sediments contain organic compounds and cadmium. A dose response relationship was found between cadmium concentration and metabolic activation of benzo[a]pyrene and other carcinogens (Rodriguez-Arita 1994).

Since air pollution is always mixed, the effects of organochlorides and other toxic compounds cannot be separated from the co-exposure to cadmium. Many of these substances like dioxins, pesticides and herbicides bind to the estrogen receptor (Thornton 1993). Estrogen increases the uptake of cadmium into the liver, mammary glands, and kidneys (Nishiyama 1988). Cadmium 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, for instance, cadmium exposures can result in fewer conceptions and more frequent spontaneous abortions (Gerhard 1992). The toxic effects on wild life coming from exposure to chemicals that

bind to the estrogen receptor resulting in malformations, glandular disturbances and immune alterations must be assumed to be influenced by the co-exposure to cadmium which increases the levels of these toxic compounds in their tissues.

A variety of chemicals antagonize cadmium cytotoxicity in a model system developed by Shopsis (1994). These chemicals induce differentiation.

Dimet hylsu If oxide (DMSO) added 6 hours after initiation of a 24 hour exposure to cadmium was protective but with prior exposure and then removal there was no protection. DMSO did not induce or increase the concentrations of metallothionein or glutathione in the cells. There is a new class of agents, the 21-aminosteroids, which inhibit iron-dependent lipid peroxidation. These chemicals block effects of cadmium but have not yet been studied directly with cadmium. A chemically induced pulmonary fibrosis was blocked by a 21- aminosteroid (McLaughlin 1994).

Many pharmaceutical drugs block actions of cadmium or make cells less susceptible to its toxic action. Cadmium in turn affects their metabolism and very likely their toxicity. Individuals with extraordinary sensitivity to environmental chemicals, drugs and foods can be expected to be sensitive to the toxic action of cadmium.

Global Issues:

Problems. Although cadmium can affect all cells, it has not yet been intensively studied in environmental problems and human disease. Consequently, any discussion of its effects in global biological systems is speculative. However, since there is evidence for a global increase in cadmium exposure, global environmental problems influenced by biological

systems, diseases of unknown etiology that are increasing and infectious diseases that are increasing should be suspected of having an interaction with cadmium using the precautionary principle.

The availability of zinc powerfully affects the interactions between cadmium and the cell surface receptor that influences inflammation and carcinogenesis. For this reason, it is concerning that Showman (1989) found that zinc levels in air over the years 1973 to 1988 had fallen (as measured in lichens). This could come from a cadmium-induced decreased uptake of zinc into plants and subsequent release into air (Beauford 1977).

Global Warming. The extreme sensitivity of cells to cadmium in a setting of zinc deficiency makes global cadmium air pollution so potent. During the period of intense lead pollution, the global warming trend which began to accelerate in this century, slowed and even reversed itself for a short time (Baliunas 1995). In a study of tree rings of a single oak tree (Hagemeyer 1993), cadmium levels, which were inhibited for a few decades by the lead pollution, form a curve that matches the dip in global warming. See Figure below, the insert is the tree ring cadmium in ng/g from 1947 to 1970.

One explanation for this linkage of variation in cadmium levels in a single tree and global temperature is that lead, by blocking cadmium uptake into this and other plants and subsequent return back into the atmosphere, blocked a potent global air pollutant that affects global temperature.

Cadmium's innate ability to alter biological systems makes this effect scientifically plausible. Bacteria exposed to cadmium have a respiratory burst, increasing the production of carbon dioxide and water, two greenhouse gases associated with global warming. With gradual exposure to cadmium, tolerance can develop. These adaptations can have complicated effects. Cadmium 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.

Cadmium is toxic to trees,

inhibiting roots, decreasing nutrient uptake, decreasing photosynthesis and increasing

photorespiration which also increases water and carbon dioxide production (StewartPinkham 1991 a). By making trees vulnerable to injury and disease, cadmium promotes forest declines, further increasing global warming.

Viral Activation. With the HIV epidemic arriving in the time period of falling lead pollution and rising cadmium pollution, it would be most helpful to know whether cadmium 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 cadmium toxic effects, or enhance its excretion, also block the replication of HIV (Stewart- Pin kha m,] 991 b). 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.

Cadmium is the only metal that activates Herpes simplex from a latent state (Pawl 1993). Continued administration of cadmium increases the yield of infectious virus by 10 to 100 fold, an effect unmatched by any other activator studied. It also prolongs the recovery of infectious virus from 6 to I I days. Zinc, nickel and manganese, on the other hand, block the cadmium-induced infectious virus. Likewise, lithium

blocks Herpes activation (Skinner 1980).

Bacteria. In studies of metal ion air pollution and a bacterial infection, cadmium was the most toxic of all the metals, causing 100% mortality in the mice (Gardner 1977). Cadmium exposure induces tolerance in bacteria, a process associated with plasmids where virulence factors are encoded. With virulent strains of Streptococcus gaining attention it would be important to know if it is inhibited by lead and promoted by cadmium. From 1968 to 1983 the rate of Streptococcal-induced Rheumatic Fever in the industrial world exposed to lead pollution was very low. Since then increases have been noted.

There is much that is unknown regarding cadmium's effects on biological stressors and the impact of increasing global cadmium air pollution on the global environment and human health. It is particularly difficult to identify controls when attempting to detect impacts of cadmium air pollution on environmental problems like forest declines or changes in human health (Stewart-Pinkham 1991). Areas of geological mineral excesses or deficiencies are more vulnerable to toxic effects of cadmium at a given level of exposure. 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 (Jamall 1989). There are large areas

of the world with selenium deficiency that can be expected to have heightened sensitivity to cadmium air pollution, including large areas of the former USSR (Ermakov 1992), parts of China, Yugoslavia (Maksimovic 1992), and Christchurch, New Zealand (Sluis 1992).

The New Morbidity. Sinusitis and chronic fatigue are two common problems that are increasing in our population. Two studies which involved exposure to cadmium and nickel in battery factories provide some perspective on the kinds of effects one could expect from a global increase in cadmium exposure. In one 637o of individuals exposed to cadmium fumes had sinus x-ray abnormalities compared to 33 % in the general population (Shoham 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, out of 38 individuals who had a CT scan 6 had brain atrophy, one died of lung cancer, one died of pancreatic cancer, and one died of leukemia (Bar-Selo 1992). Similar

respiratory symptoms were found in a community exposed to volatile organic fumes (Ozonoff 1987).

These studies illustrate the wide variety of symptoms and diseases cadmium exposures can produce with other substances that cause synergistic toxicity. Such multi-system problems share much in common with problems of undetermined etiology that appear to be increasing like Chronic Fatigue and Environmental Chemical Sensitivity (Stewart-Pinkham, 1990a). Individuals with these problems are being exposed to increased levels of cadmium pollution in conjunction with other exposures from metals, organic chemicals, and biological stressors. Their symptoms suggest senstivity to toxic effects and an inability to adapt to stress. Unfortunately, in large populations there will be a significant minority with persistent sensitivity to cadmium. These individuals often have a low levels of cadmium in their tissues because they lack the ability to efficiently bind and detoxify cadmium (Shore 1994).

Reproductive Failure. 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 cadmium air pollution (Sloof 1991). These beavers had the lowest population growth of released beavers in Europe (Nolet 1994). Thirty percent of

this highly toxic metal ion in the stress response to rid themselves of damaged, infected, and cancerous cells. By producing chronic stress at a cellular, organ, and individual level, cadmium increases the risk of birth defects, multiple organ damage, premature aging, substance abuse, societal violence, and cancer, not alone, but by increasing the effects of all other stressors.

Cadmium has complicated interactions with other metal ions and chemicals. Additions of metal ions, like lead and aluminum, and organic chemicals, like ethanol, can increase cadmium absorption and lead to cadmium toxic effects.There is suggestive evidence that cadmium contributes to global warming, forest decline, increased virulence of infectious diseases, and a rise in disabling fatigue and reproductive failure.

Implications For Public Policy:

Limit Exposure.

Limit global population growth.

Preserve forests, especially the complex ecosystems in rain forests, which protect the entire planet from the stress of increased cadmium exposure.

Use bio-technology to sequester metals and break down organic pollutants (Raraz 1995).

4.Stop pollution at its source. Collectively, we need to protect our environment from an onslaught of

4. chemicals.

Limit the allowable level of cadmium in cigarettes. This single step would greatly decrease the toxicity of cigarette smoke, both active and passive.

Educate

4. Motivate the public to avoid the use of tobacco, alcohol, drugs, and a bad diet and so reduce the incidence of disease.

4.

Advise parents to protect their children from passive cigarette smoke.

5.

Advise teenagers that cigarette smoking, alcohol use, illicit drugs, and a poor diet can adversely influence their health as they age and increase their risk of having children with birth defects or having reproductive failure.

Change Medical Managment and Research.

4. Evaluate patients biochemically in a comprehensive manner.

5.

Determine cadmium sensitivity of cancer cells prior to selecting therapy.

4.Supplement deficient nutrients, like magnesium, zinc, selenium and lithium.

5.

Address life style issues, including diet, exercise, and emotional stress.

6.

Study traditional medicines in use for centuries, like licorice, garlic, and fungi.

7.Study cadmium effects in freshly biopsied cells, which were shown by Pool-Zobel (1994) to be very sensitive to cadmium, rather than in cell lines that may have already acquired

4.

cadmium resistance.

6. In molecularly based studies, use the hypothesis that free cadmium ions has many effects on cell processes in both genetic and acquired disease.

Cadmium acts as a "chaos" factor, so changes can 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 19906). 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 make use of beneficial effects of cadmium while reducing the harmful impacts of cadmium air pollution.

References:

Abrahams W, Tranter 10, Davies TD, Blackwood !L, Landsberger S. Trace-element studies in a remote Scottish upland catchment: I . Chemical composition of snow and melt waters. Water Air Soil Bull 1988;37:255-271

Adebayo GI, Gaffney P, Buggy D, Feely J. Acute inhibitory effect of alcohol on sodium-lithium countertransport. Alcohol 1994:11:367-370

Ahner BA, Price NM, Morel FM. Phytcchelatin production by marine phytoplankton at low free metal concentrations: laboratory studies and field data from Massachusetts Bay. Proc Nat Acad Sci USA 1994;91:8433-6

Anderson 0, Nielson JB, Nordberg GF. Factors affecting the intestinal uptake of cadmium from the diet.]ARC Sci Publ 1992(l] 8):173-187

Anke M, Arnold W, Groppel B, Krause U. The biological importance of lithium. In Lithium in Biology and Medicine, GN Schrauzer and K-F Klippel beds). VCH: New York, 1991

Baliunas S. Global warming: why the data matter. SETAC News 1995:15:21-23

Bar-Selo S, Levy M, Westin JB, Laster R, Richter ED.
Medical findings in nickel-cadmium battery
workers. Israel J Ivied Sci 1992;28:578-83Beauford W, Barber J, Barringer AR. Release of particles

containing metals from vegetation into the atmosphere. Science 1977;195:571-573

Berglund M, Lind B, Lannero E, Vahter M. A pilot study of lead and cadmium exposure in young children in Stockholm, Sweden: methodological considerations using capillary blood microsampling. Arch Environ Cont Toxicol 1994;27:281-7

Bin QH, Garfinkel D. The cadmium toxicity hypothesis of aging: a possible explanation for the zinc deficiency hypothesis of aging. Medical Hypotheses 1994;42:380-384

Blazka ME, Shaikh ZA. Cadmium and mercury accumulation in rat hepatocytes: interactions with other metals. Toxicol Appl Pharmacol 1992:113:118-125

Burger J, Gochfeld M. Tissue levels of lead in experimentally exposed herring gull (Cares cigentolus) chicks. J Tox Environ Health 1990;29:219-233

Chan HIA, Tamura Y, Cherian MG, Geyer RA. Pregnancy-associated changes in plasma metallothionein concentration and renal cadmium accumulation in rats. Proc Soc Exper Biol Ivied 1993;202:420-427

Chaumard C, Forestier F, Quero AM. Influence of inhaled cadmium on the immune response to influenza virus. Arch Environ Health 1991;46:5056

Chiocca SM, Bigert NW, Murphy EC. Molecular mechanisms in metal carcinogenesis. Targeting of mutations to retiovirol genes (meeting abstract). Proc Ann Meet Am Assoc Cancer Res 1989;30:A740

Chishti MA, Rotkiewicz T. Hepatic and renal ultiosttuctural changes in cockerels exposed to cadmium chloride and subsequent interaction with organophosphate insecticide. J Environ Pothol Toxicol Oncol 1993:12(1):35-45

Clark JT, Jimenez B, Evans SL, Barrow R, Winfree H, Mrotek JJ. Cadmium-induced sexual dysfunction does not involve increased hepatic metabolism of testosterone nor increased circulating levels of corticosterone. Physiology and Behavior 1994;56:975-981

Cody CW, Huang PC. Ivietallotheionein detoxification function is impaired by replacement of both conserved lysines with glutamines in the hinges between the two domains. Biochemistry 1993;32(19):51 27-5131

Colborn T, Clement C. Chemicall^{y}-Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection. Princeton: Princeton Scientific Publishing, 1992

Cook JA, Hoffmann EO, Luzio NR Di. Influence of lead and cadmium on the susceptibility of rats to bacterial challenge. Proc Soc Exper Biol Med 1975;150:741-747

Coppen-Jaeger DE, Wilhem M. The effects of cadmium
on zinc absorption in isolated rat intestinal
preparations. Biel Trace Ele Res 1989;21:207-212 Djingova R, Kuleff I. Monitoring by Taraxacum officinale.
In Plants as Blomonitois, B. Marken (ed). VCH:

New York, 1993

Durlach J, Durlach V, Bac P, Rayssiguier Y, Bata M. Magnesium and aging. II. Clinical data: aetiological mechanisms and path ophyis o logical consequences of magnesium deficit in the elderly. [Review] Magnesium Res 1993:6:379-394

Elinder CQ. Cadmium as an environmental hazard. IARC Sci Pill)] 1992(118):1232-132

Endo T. Shaikh ZA. Cadmium uptake by pr ilIIM-YCLIltLil_CS of rat renal cortical epithelial cells: influence ol'cell density and other metal ions. 'Foxieol Appl PllalllIacol 1 9 9 3 . 1 2 I l

Ennakov VV. Bio-cocliernical regioning problems and the biogeocherilical selenium provinces ill the lOrnier UVSR. Biol Trace Elem Res 199233:171 -1 X5

Evans J, Hastin$_g$S L. ACCLItIlUkiti011 ol'Cd(ll) ill the CNS delienLimp, oil the route ot'a(lininiti ation: inti alicrilonoal, ilitlatraelleal. or ilrtrallas:lL FtIIILI AI)I-i'l,oxicol 1992:1 9:27S-278

Pawl Rl- Roizimin 13. Induction ol)Qactivzition ol-herpessiIIII)ICx VIRIS III IIIUrIIle sensory t!ZiiIIKl in vivo h,\'Cu(IIIliLilll. J Virol 1993:67(12):7025-7031

Foulkes EC. On the mechanism of cellular cadmium uptake. Biol Trace Ele Res 1989:21:195-200 Foulkes EC, ed. Cadmium. Handbook of Experimental Pharmacology. Vol. 80. Berlin: Springer-Verlag, 1986

Fox G. Practical causal inferences for ecoepidemiologists. J Toxicol Environ Health 1991:4:359-374

Frankel FIR, Steeger JR, Damicno VV, Sohn NI, Oppenheim D, Weinbaurn G. Induction of unilateral pulmonary fibrosis in the rat by cadmium chloride. Am J Resp Cell Mol Biol 1991;5:385-94

Freedman 11,1[1], 1,uisi lit-. KorsZLIII /R. et al. Function and structure 01' the metal coordination sites with the gltleOCOIIICOiLl DNA binding domain. Nature 19" 334:543546

Fritierg L. Piscatoi \1, Nor(iher_g GP. KJellstrolli'l" Cadmium in the Environment. Cleveland: CRC Press. 1971

Funk AE, Day FA. I 11_3Lh 1'0. DiSj)1:11:0110111 Ol'XillC and Copper copper-induced nietallothionein I)\ cadiiii(tin and nriorctir\: lit vivo and ex VIVO StLiklICS, Comp I3iO1:IleIII I'll \'';lot C. 1987:86:1-6

1 LllltO\ViCZ So, Ra\ I'llVellailIIN. cOnIIIICxit and post-normal science. EnvironClient 1994:13: INX I - 18',X5 Gairola CG. Wegner 0.1. Cadmium accumulationl in the 1LiII1_'. liVQI and kidney \ OI'IllicO and rats chronically Q.\POsCd to ci$_g$arettesmoke. J Al)pl Toxicol 199 1 :3 5 5-3 SX Gamberg M, Scheuhammer AM. Cadmium in caribou and muskoxen from the Canadian Yukon and Northwest Territories. Sci Tot Environ 1994:143:221-234

Gardner DE, Miller FJ, Illing JIM Kutz JM. Alterations in bacterial defense mechanisms of the lung induced by inhalation of cadmium. Bull Environ Physiopathol Resp 1977:13:157-1

Carty J. Lichens as biomonitors of cadmium. In Plants as Biomonitors, B. Markett led). VCH: New York, 1993

Gerhard I. RunneliaLini B.'I'lie limits I)t'hormone substitution in pollutant exposure and leftilif ' N (11.101-110S. ZelltlAlfl Gynakol Nnakol 1992:114(2):593-602

Ghost A. CjrCelll)0rg.\l. Calcium sil 1:111111" ill neurons: r101eellkll

111"llMli.1nIS and cellular COIlseluCIICCS. Science 199 5:268:239-247.

Gordon C.I. Fogelson L. Highlill JW. 11\1)otlicniiia and IINI-iolnetaholism: sensitive indices ot'Whole-body toxicity 1'01IO\6lgCXI7)Os*LII'C to metallic salts in the mottle. J Toxicol Environ Health 199U9185-200

Goyer R.A. Lead t,)Nicit\: current concerns. [Review] Environ Health Persil 1993A00:177-87

0-inihIc RI'. Nutritional antioxidants and the modulation Of ini'lanimation: flicor ' N and practice. [Review] New horizons 1994t2-175-Xs

Gupta A. Whitton B.A. 1\101-1) V AP. I ILICklC JW, Robinson NJ. Alllplil!:alioll and rearrangement ol'a prokaryotic IlletJ110111i0eill locus ';lilt in S\'nCdhocOCCUS PCC 6301 selected rot tolerance to cadmium. Proc R See Lord Biol 199224X:273-28I

I el- J. Monitoring trace metal pollution with tree rings: a critical reassessment. III Plants as Biomonitors, B. Markett led). VCH: New York, 1993

11,ilm P. 11\\crs U. Jermaril l`,. Frowi 1. 111-0eklIZILIS A, Schlipkoter I I\\'. Cadmium kidney cortex or inhabitants ot'NorthWest GonliaIlY: its relationship to age, sex, smoking and environmental pollution by cadmium. intern Arcll Occup Environl health 1 987:59:1 6 i- 176

I IMIM(lZi '1'. "IZI111111010 A. IX\ ai S. I`Li.ii\\ Zil ZI 11. SasZIP'ul i Y.

C\ tol'alllologicll changes induced hY cu(111111.1111-exposure lit canine proximal tubular cells: a c\loclieniical and ultrastruClural StUI \ . Nelflit oil 1 994:68:1 04-111

1 Lit [.,[i"W .1 K I$_t$ - Leo \I- N lol eI .1(; el al. Statistical analysis orthe elle,A 01 cadmium and zinc on hamster teratogellesis. Biodietn XIc'd Metal Hicil 1992AS:1 59

Hartwig A, Beyersmann D. Co-mutagenicity and inhibition of DNA repair by metal ions in mammalian cells. Biel Trace Element Res 1989:21:359-365

llazelli,,I1'Ro,Ifzeni:i W, Roololsen A\I. Ifeil-ier RP. Leone W, Copius- lit. I- ' llects ol'cl)[-011ic cadmium administration oil placental and fetal dc\el')I)IIIent.,Thrace 1.16'111 Electrolytes health Dis 1 987: 1(1):49-53

Heckman CA, Murphy EC Jr. Analysis of cadmium-induced mutations altering conditionally defective cell transformation by IvIUSVTSI 10 meeting abstract). Proc Ann Meet Am Assoc Cancer Res 1992:33:A686

Ile1nt'rich R. CIlall"Cs
, ill cadmiumof

*I*q xr si,[1]vatical_ with increasing altitude. In Plants as Biomonitors, B. Markett fed). VCH: New York, 1993
I lertzi" R. Multi-residue anal[y]sis \\itli passive hionlonitoring: a new approach I'M volatile multi-element contents, heavy metals and 1101 ' NC wlic aromatic 11\Llrocal-11011" with lichen
S\\itzejl:iti(l and the principalit[y] v ot'Lichtenstein. In Plants as Biomonitors, B. Markett led). VCH: [',[l]ew Yoi k, 1993
11 i(lalgo J. . \l-lnal io A. 1-111"M Of'eaLIJI)IIIIII Oil pituitary adrenal axis. 'I'ONi0)IO1'\'
, I 987i54:1 13-116
1 li-lak.-) J. Gildlt \l. Garve[y] JS.:Armari1) A. SCN and restraint &111,renco, i[ll] rat nielallothioiiQin and zinc levels. Rev Esp l'isiol 1987i43:427-432
I londa K. I hI3\:IIMl 1'. 'I'ZlkAl3.1Ili K.)`Liki0ka M. heat shock
proteins III human and IIIOLISe embryonic cells alter
exposure 10 heal shod, or teI_ZItOi',ClUC agents.
'Fera10"ClIOSIS CM-Cill0[6] \lLItZI"CII-244
199 1:11 (5): 235-244 I Seeman F.I'W
F. 'I'Il,: hone dQrIsitYO1eIMII0ills discordant tobacco use. N Eliot J Me(l 1994:330:387-392

28

Jadhao AG. Paul Pl_ Rao 1[1]1). Effect ofcatimium chloride on the POLHUIIX, Ill [illegible]

b~ilmclilis Function N.' Developmental Morphology 1994:4:39-44
Jam,ill IS, Roque 1-1. CadiniLlin-induced alterations in ocular traCO elCII)ClAS. Influence 01'tlieUll-N selenium and copper. Biol 1'nicc F ' lein Res 1989-9U3: S S-63
Jayaskera R. Concentrations OfselcOod heav[y] metals in different C0111IM11111ClltS of mountain rain loleSt ecosystem in Sri
Lanka. In Plants as Biomonitois, B. Maikett led). VCH: New York, 1993
Kajiinieng:i JE, Van Gestel CA, l3ekkcr .1. Patterns of sensitivity to cadmium and penuichloroplienol inioiig nematode species from ditlerent tZINOTIOMic and ecological groups. Arch Environ Cons 'I'ONiCOI 1994:27:88-94
Koizumi T, Suzuki KT. Cellular pH and the cytotoxicity of heavy metals. Biomed Res Trace Elements 1994;5:9-24
Koizumi T, Yokota T. Shirakura H, Totsumoto H, Suzuki KT. Potential mechanism of cadmium-induced cytotoxicity in rat hepatocytes: inhibitory action of cadmium on mitochondria) respiratory activity. Toxicology 1994;92:115-125
Koizumi T, U ZG. Role of oxidative stress in single dose, cadmium-induced testicular cancer. J Toxicol Environ Health. 1992:37(1):25-36
Kowa) NE. Urinary cadmium and beta 2-microglobulin: correlation with nutrition and smoking. J Toxicol Environ Health 1988:25:179-183
Lai YL, Diamond L. Cigarette smoke does not prevent cadmium-induced alterations in rat lungs. J Toxicol Environ Health 1992;35:63-76
lag M. Hegeland K. Effects ol'cakfimuni and other metals on ciliary activity of MOLISe trachea organ culture. Phnom To\icol 1987:60:318-320
Lagerkvist B.I. Noall)crg (;l', Soderberg I IA_ Ekesr,01i S. 1-.ii,,I.\st
GLINtft\'SSOII M, Gusta[y]son NO, Wiklund DF. Placental
trzoistcr of cadmium. IARC Sci Buhl 1992(1 1 8):287-291 tanning X. \VIIolc 0111111[1].[y]o Illorpliorlicil-N ill terolo-ell screenill".
'Foratolog\. 198736:2()~-270
Lehmann K. Endogenous lithium levels. I)I)ZIIIIIZICOpsyCl)MII_\ 1994.27:130-132
Leonzio C. Foss MC. Lari 1- Foc:irdi S. Influence ol'caLlnmml on poIvCIjIOI'0l)1I)IIejl\I uptake. \IFOilcIi\lt\. ZIlldscililll lipid levels in Japanese quail Aida Environ Contain Toxicol 1992:22(2):238-241
Lockett CJ, Leary WP (1986): Neurobehavioral effects in rats fed low doses of cadmium and lead to induce hypertension. S. [A]r[t] Ivied J 69:190-192.
Lohmann RD, Beyersmann D. Cadmium and zinc mediated changes of the Ca (2+)-dependent endonuclease in opoptosis. Biochem Biophys Res Commun 1993;190:1097-1103
Lutz W. Preliminary studies of the effect of diseases and environmental pollution on the population dynamics of wild rabbits (Oryctolagus cuniculus Linnaeus, 1758) in the federal state of North Rhine-Westphalia (Germany). Rev Sci Tech 1993 MaO 2(1):27-34
Maksimovic ZJ, Djujic I, Jovie V, Rsumovic M. Selenium deficiency in Yugoslavia. Biol Trace Elem Res 1992;33:187-196
Manca D, Ricard AC, Tiotfier B, Chevalier G. Studies on lipid peroxidation in rat tissues following administration of low and moderate doses of
cadmium chloride. Toxicology 1991;67:303-323
Martin Mateo MC, Rabadan J, Boustomante J. Comparative analysis of certain metals and tumor markers in bronchopulmonory cancer and colorectal cancers. Metals and tumor markers in the neoplastic process. Clin Physiol Biochem 1990;8:261-266
McLaughlin GE, Frank L. Effects of the 21-aminosteroid, U74389F, on bleomycin-induced pulmonary fibrosis. Critical Care Medicine 1994;22:313-319
Melichoi B, Aichberger C, Artner-Dworzac E, et al. Immune activation and enhanced urinary zinc concentrations in allograft recipients. Presse Medicate-Paris 1994;23:702-706
Nlic,::ulci S. Florid] A. Sites of inhibition ol'iiiitocliondiral electron transport by v cmililiull). clleolico-Biological Interactions 1993:89(2-3):1 ~9-1 67
Mislin H, Ravera 0 (Eds). Cadmium in the Environment. Experientia Suppl 1986;50: Birhauser Verlag, Boston/Basel.
Mlychara T, Takata M, Mori-Uchi S, Muyata M, Nagai M, Sugure A, et al. Stimulative effects of cadmium on bone resorption in neonatal parietal bone resorption. Toxicology 1992:73(l):93-99
Morales AJ, Nolan JJ, Nelson JC, Yen SS. Effects of replacement dose of dehydroepiandrosterone in men and women of advancing age. J Clin Enclocrinol Metab 1994;78:1360-1367
\1.\I\\ R. alcohol- and other drug use among high school students--united St:itL:,;,] 991. \lorl)iklrt\ and Mortality \\'eakl[y] RC1101-1. 1992i41:698-703
Morgan I I (eel). 'hie s1lipliialli report. all investigation into cadmium contamination and its implications for health. Sci Tot I' 1s' , . ' n\ iroii 19Si7~\tigust I ;
MTP

u·CIIT, DCillliCr.l\V. sodium-l)ic;lrl)oIIZIle cotialls'poll current in identified leech filial cells. .1 Ol')ll\.1iOIO_gy- London 1994:474:43-i3

.\ILI]tll\ Ilolocack M.I. t'III-*stI-tI1:IUFA changes in rat lungs "q)oscd to combinationsot'cztcfiiiiitiiii. ziiic, copper, and nicker J Stillillicloscopic Cytology & Pathology 1991 i23:210-293

Nation .1R. Baker D%I. Brattoti GR, et al. F Iliziiiol self-administration Ill rats Billowing exposure to dicta-\' ezi(lillitilli. Tel atol 1987i9:339-344

Nalion.[R. h\c (;I)- Von SlUlt/. J, cl al. FIIcels ot'confliiiied lead and rlL1111111111 exposure: changes in schedule-controlled responding and in dopamine. ser otonin. and their metabolites. Illia\ NeIll-OsCi 1989-103:1108-1114

Nislikztiiia S. OiiosaiU S. Taotislii T. et al. Stimulation ofcaCl[lIii1nI uptake l)VQsllaLl10l in the kit-Il)OV01*111:11C rats treated kith Cadliliuili. Biochem Plim-nizkcol 198837:3091-3096

Nocentini S. Inhibition of DNA replication and repair in mammalian cells. Protective interaction of zinc. Nucl Acids Res 1987:15:4211-4225

Noda H, Sugivama M, Tatsumi S, Sano Y, Konishi S, Fututcni A, Yoshimura M. Study on secular changes of cadmium concentration accumulated in main organs of Japanese. Hippos Hoigaku Zasshi 1993;47(2):153-159

Nolen BA, Dljkstra VA, Heidecke D. Cadmium in beavers fianslocated from the Elbe River to the Rhine/Meuse estruary, and the possible effect on population growth rate. Arch Environ Conf Toxicol 1994:27:154-161

Nordberg GF, Herber RFM, Alessic, L leas). Cadmium in

1991 ; 121:87-91
Sharma RP, Kjellstrom T, McKenzie JM. Cadmium in blood and urine among smokers and nonsmokers with high cadmium intake in food. Toxicology 1983;29:167-171
Shipp MA, Stefano GB, Switzer SN, Griffin JD, Reinherz EL. CD10 (CALLA)/neutral endclpeptidase 24.11 modulates inflammatory peptide-induced changes in neutrophil morphology, migration, and adhesion proteins and is itself regulated by neutrophil activation. Blood 1991 ; 78:1834-41
Shopsis C. Antagonism of cadmium cytotoxicity by differentiation inducers. Cell Biology & Technology 1994:10:191-205
Shore RF, Douben PE. The ecotoxicological significance of cadmium intake and residues in feitesticl small mammals. Ecotoxicology & Environmental Safety 1994;29:101-112
Showman RE, Hendrick JC. Trace element content of Flavoparmelia caperata (L.) Hale due to industrial emissions. J Air Poll Conti Assoc 1989;39:317-320
Shukla GS, Chandra SV. Coincidental exposure to lead, manganese, and cadmium and distribution to various brain regions, liver, kidney, and testes of grown rats. Arch Environ Cont Toxicol 1987;16:303-310
Skinner GRB, Hartley C, Buchana A, et al. The effect of lithium chloride on the replication of herpes simplex virus. Med Microbial Immunol 1980;168:139-148
Skoczynsko A, Smolik R, Milian A. The effect of combined exposure to lead and cadmium on the concentration of zinc and copper in rat tissues. Internat J Occupof Med & Enviion Health 1994;7:41-49
Sloof JE. Patterns in trace elements in lichens. Water, Air, and Soil Pollution 1991:57-58:785-795
Slurs KB. Darlow 13A. George P\I.N. Dolanwic B.A. W i lite] hou ni CC. Selenium and glutathione pelo\idaw levels in premature illlSllts in a low selenium community (Christchurch. Nevi Z"ilandr. Ped Res 1992:32: 1 N9-194
Smith CA- N'l Ji . 0 1) AC. Spurr NK_ Wall CR. lerular genetcana-sisdhe.ytochrome\110domeP4-0(1611SO(L1111Cli\'do.\;NLise SLISCCl Environ IleAlll perspectives 199198:107- 112
Smith JB. Dwyer SI). Smith L. Cadmium evokes illll illfl polyphosphate f'onlialion :lid calcium mobilization. Evidence fur a cell sulfite,: receptor IllZil. cadmium stimulates and zinc ZIM,,1011 14CS. J H101 Chem 19,'Q264:71 15-71 IS
Sinilh.0 Smith L. Pijuan V. 7,11LIZIll, Y. Olen Y-C. 'Fralilliellibrallo signals anti I)I-otooneogene indLl,:11011 evoked 1,\ carcinogenic metals anti prevented I)\ zinc. I- ' n\ non I lealth Pei, 1994A02 (SLlil)l 3) 1 X] -189
sovellyi J, Szakolc/,ai J. Studies on the and mllllLill0Slll)I)ICSS1\O ellccts ol'cadmiuni on the common carp. Acta \ et I I Lill 1:11-1 Ca 1993AIAI ~-426
Staessen J, Yeoman WB, Fletcher AE, et al. Blood cadmium in London civil servants. Intern J Epidemiol 1990;19:362-366
Staessen J, Bernard A, Buchet JP, Cloeys F, Dekempeneer L, et al. Effects of cadmium exposure on the cardiovascular system and on calcium metabolism: results of a cross-sectional population study. IARC Sci Publ 199211181:263-269
Staessen J, Lauwerys R. Health effects of environmental exposure to cadmium in a populates StUdy. J }loin 11%porlonsion 1993i7(2)195-199
Stewart-Pinkham SM. The effect of ambient air cadmium pollution on the hair mineral content of children. Sci Tot Environ 1989a:73:289-296
Stewart-Pinkhom SM. The relative role of lead and cadmium in disease. Internat J Biosocial and *Med* Res I 989b: 11 (2):121-133
Stewart-Pinkham SM. Chronic fatigue syndrome: is cadmium the catalyst? Inter J Biosoc Med Res 1990a; 12 (1):21-35
Stewart-Pinkham SM. The toxicity of cadmium air pollution: a reappraisal. J Environ Geochem and Health, Suppl 1990b; 12: 345-369
Stewart-Pinkinam SM. Detecting ambient cadmium toxicity in an ecosystem. Plants for Toxicity Assessment: Second Volume, ASTM STP 1115, JW Gorsuch, WR Lower, W Wang, MA Lewis, .Eds. ASTM, Philadelphia, 1991 a, pp 161-171
Stewart-Pinkham SM. The progression of HIV to AIDS: is cadmium playing a catalytic role? Trace Substances in Environmental Health 1991 b;24:81-9 7
StiaZ71jjjo P, Cappuccio FP, Miller MA, et al. Erythrocyte sodium-lithium countertransport: relationship with plasma resin activity, aldosterone and atrial natriuretic peptide in a population study. J of Human Hypertension 1994;8:199-204
Sugawara N, Sugawara C. The effects of aluminum ingestion on intestinal cadmium absorption, lipid peroxidation, and alkaline phosphctose activity. Toxicol Lett 1992:61:225-232
Sung S, Asokawa F, Jitsunari F, et al. Assessment of cadmium and lead released from cigarette smoke. [Japanese] Nippon Eiseigaku Zasshi Japanes J Hygiene 1991;46:1014-1024
Szczypka MS, vliemrnie JA, Moye-Rowley WS, Thiele DJ. A yeast metal resistance protein similar to human cystic fibrosis transmembrane conductance regulator (CFTR) and m(jlt:diug resistance-associated protein. J Biol Chem 1994;269:22853-7
Takeda A, Norris JS, Iversen PL, Ebadi M. Antisense oligonuclectide of c-myc discriminates between zinc and dexamethasone-induced synthesis of metallothionein. Pharmacology 1994:48:119-126
Tehseen Wlvl, Hansen LG, Schaeffer DJ, Reynolds HA. A scientific basis for proposed quality assurance of a new screening method for tumor-like growths in the planarian, Dugesia dorotocephala. Quality Assurance 1992; 1:217- 229

'1101-11][011.1. Chlorine. human health and the environment.
O·"eill,eace, W Isliiji,_·Ion. DC'. 1993
Valltet NL 11Q1·1tilitl NL Slorach S. J011leffl I_ I R. Integrated personal monitoring Ot',:Mllllli1lll1 exposure ill Sweden.