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The challenge posed to children's health by mixtures of toxic waste: the Tar Creek Superfund Site as a case-study

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I. Introduction

In the United States, many of the millions of tons of hazardous wastes that have been produced since World War II have accumulated in sites that are scattered around the nation. At first, people were relatively unaware of how dumping chemical wastes might affect public health and the environment. On thousands of properties where such practices were intensive or continuous, the result was uncontrolled or abandoned hazardous waste sites, such as abandoned warehouses and landfills. Citizen concern over the extent of this problem led Congress to establish the Superfund Program in 1980 to locate, investigate, and clean up the worst sites nationwide. The Environmental Protection Agency (EPA) administers the Superfund program in cooperation with individual states and tribal governments. Over 15,000 such sites have been identified by the EPA across the United States, around 1,400 of which are on the National Priorities List (NPL) and thus recognized as posing significant potential risks to health (1). These sites are of a diverse nature, ranging from open pit lagoons of liquid toxic wastes to abandoned mines, dumped pesticides, aquifers contaminated by leaking gasoline storage tanks, etc. Of the 11 million Americans that are estimated to live within 1 mile of such sites, 3 to 4 million are children under 18 years of age (2).

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What are the risks posed to children by toxic or hazardous waste? One of the most vexing challenges that arises when attempting to address this question is the realization that most such waste exists as a complex mixture of many substances. Wastes are rarely segregated; most often, they are dumped together into pits or ponds, added to piles, etc, from which human exposure can eventually occur in the form of multiple contaminants in drinking water, airborne dust, crops, and other media. On the other hand, the vast majority of what is known about chemicals and risk has been derived from single exposure studies---i.e., experimental studies in animals of individual toxic agents, or in human population studies that focused on the relationship between individual exposures and adverse outcomes (3). Such knowledge may not be sufficient to predict the toxicity of mixtures, since evidence is mounting that interactions may occur between toxicants on many levels that, in some cases, have the potential to greatly magnify toxicity.

In this paper, we will discuss the issue of toxic mixtures and children's health by focusing on the specific example of mining waste at the Tar Creek Superfund Site in Northeast Oklahoma. Mining sites— active, inactive, or abandoned— constitute a major category of Superfund NPL sites that is growing in volume. The Mineral Policy Center estimated in 1995 that, nationwide, there were 557,000 abandoned mines. Most present minimal human health risks, but many do and of the 1,400 sites on the NPL, 19 were identified as mining "megasites". Overall, the cost of cleanup for such sites has been estimated by the EPA at over $24 billion.

At the Tar Creek Superfund Site (TCSS), one of the nation's largest such sites, over 40,000 residents live in a 50 square mile area filled with mining waste containing lead, manganese, cadmium, and other potentially toxic metals. The TCSS has been the subject of two major on-going studies undertaken by the authors and colleagues with support from the Superfund Basic Research Program and the Center for Children's Environmental Health and Disease Prevention Research at the Harvard School of Public Health. We will use the TCSS as an example to discuss issues related to the multiple pathways through which toxic waste mixtures may gain access to the immediate environment of children (or fetuses); factors that may influence absorption of mixtures once ingested or inhaled; the vulnerability of children's developing organs to mixtures; lessons for clinicians; and research needs.

II. The Tar Creek Superfund Site: Mixtures of Metals

Background

The Tar Creek Superfund site, also known as the Picher Lead/Zinc Mining District of northeastern Oklahoma, was one of the world's largest lead and zinc mining areas. Mining activity in this area began in 1891 and continued up until the 1970's, during which an estimated 1.7 million tons of lead and 8.8 million tons of zinc were produced. It is now one of the largest Superfund sites in the U.S., with an area of nearly 50 square miles and estimated costs of remediation and monitoring ranging from $540 million to $61.3 billion (4). The site was listed on the EPA's Superfund National Priority List on September 8, 1983. The site is situated in northern Ottawa County and Tar Creek is the principal drainage system for much of the area, passing through many of the towns before emptying into the Neosho River, one of the two major rivers in northeastern Oklahoma.

Beneath approximately 2,500 acres of this site lie around 300 miles of underground tunnels, and more than 1,300 mineshafts. Thousands of test borings are scattered throughout, many of which are still open. The Boone Formation was the source of the metal ore and is also an aquifer. When mining operations were active, large volumes of water were pumped from the mine workings until mining ceased. Since then, the aquifer and mines began refilling, during which the native sulfide materials, which had been oxidized by exposure to air, dissolved,

creating acid mine water. By 1979, water levels had increased to the point that the acid mine water began discharging at the surface from several locations, severely impacting Tar Creek.

Much of the surface of the Tar Creek Superfund Site is an alien landscape that is notable for mounds of mine tailings, also known as “chat” piles. Some are small, and some are huge; they contain an estimated 165 million tons of waste covering 2,900 acres. Many of these tailings piles are immediately adjacent to residences and schools. Some two-thirds of the nearly 300 original chat piles have been partially excavated, with the wastes used as fill and road gravel in the district and surrounding areas (4). Some of the chat was used as fill in the yards of residences and school playgrounds. The piles themselves are an attraction for local residents. Children in particular are drawn to play and bike on the metals-laden tailings piles, many of which rise 100 or more feet above the ground.

Metals also exist in approximately 800 acres of former flotation ponds that were used to extract metals (5). Metals from the acid mine water directly contaminate surface water; metals are also available to leach into the Roubidoux Aquifer, the regional water supply, by downward migration of acid mine water from the overlying Boone Aquifer through abandoned wells and boreholes connecting the two. Metals can also runoff during rainfall, and blow into breathing zones with the ever-present Oklahoma winds. Further dispersion no doubt occurs as vehicles crush the waste used as road gravel, converting it into airborne road dust.

Nine Native American tribes (Cherokee, Eastern Shawnee, Miami, Modoc, Ottawa, Peoria, Quapaw, Seneca Cayuga, and Wyandotte) are represented in the communities located within the boundaries of the Tar Creek Superfund Site, making ethnic disparities in exposure and “environmental justice” important dimensions to the environmental health problems confronted in this area. Of note is that many of the cultural practices of the people who live in this area are heavily dependent on the land. This means that toxicants that affect the water and vegetation that lie downstream from the heavily-contaminated Tri-State Mining District can be expected to disproportionately affect Native Americans, who choose to follow traditional lifestyles, emphasizing consumption of local food and water.

Exposure information

Environmental sampling has clearly demonstrated high levels of lead, cadmium, and iron in various environmental media in the TCSS. For example, in comparison to a control community outside the TCSS, Picher, a town within the TCSS, was found to have mean levels of metals in yard soil that were 8 times higher with respect to lead (851 v. 69 mg/kg, respectively), 10 times higher with respect to cadmium (34 v. 3 mg/kg) and over 10 times higher with respect to iron. Similar results were found for garden soil (6). In 1996, a U.S. EPA emergency response team found that 65% of soil samples from over 2,000 residences in the TCSS had lead concentrations >500 ppm, the action level (7).

Some environmental sampling has also found high levels of manganese. In analyses of mine water by Christenson et al. (8), the median value for levels of manganese was found to be 1,870 μg/L with a maximum value of 15,000 μg/L, several orders of magnitude higher than the maximum tolerable level of 50 μg/L set by the U.S. EPA for drinking water. Water taken from a sample of 16 Boone boreholes was also found to have high manganese levels, with a mean value of 3,318 and maximum value of 9,800 μg/L (4). Manganese levels as high as 1,900 ppm have been found in sediments along Tar Creek, downstream from the Superfund site in Miami. Well water taken from the Roubidoux aquifer has been found to contain manganese levels with a maximum value of 4,400 μg/L, with over 5% of values exceeding 1,910 μg/L (4, Oklahoma 2000). In a separate study conducted by the U.S. Geological Survey, water from 14 wells in Ottawa County had manganese levels ranging from 150 to 9,800 μg/L with a median value of 3,000 μg/L (9).

An initial set of air samples that were taken near the chat piles at Picher, Oklahoma, did not disclose high levels of toxic metals (10). However, relatively few samples were taken, and the possibility remains that air born metals are a problem away from the chat piles, where, for example, chat is used as road gravel and vehicles crush chat into finer, more respirable particles.

III. Metal Mixtures and Kids: Exposure and Dose

How might kids be exposed to the mixtures of metals that comprise mining waste? The chemistry of acid mine wastes can be complex, and as the sulfide minerals oxidize, metals can potentially be released into the surrounding environment. Thus, in addition to being a potential primary route of metals exposure, mine tailings may also be a source of bioavailable metals in areas surrounding mine wastes to which humans may eventually be exposed through water, food, and air particles.

In order to understand the risks associated with metals in mine wastes, it is important to first understand the chemical cycling of metals in mining ores as well as the bioavailability of metals in exposure media such as soil, water, indoor dust, and airborne particulates. A challenge is that the chemistry of toxic metals in mine waste piles can be highly dynamic. In parent mine waste, metals are typically present in the form of sulfide minerals, often those that were the targets of metal extraction, such as galena (PbS), sphalerite (ZnS). Weathering these minerals due to exposure to oxygen, moisture, and temperature fluctuations promotes production of acidity and sulfate and to the release of metals (11,12,13). Some of the dissolved metals released through weathering can migrate offsite with runoff. Mobilized metals also can reprecipitate *in situ* as secondary minerals such as anglesite ($PbSO_4$), cerrusite[e1] ($PbCO_3$) and smithsonite ($ZnCO_3$) and form secondary-mineral rinds on particle surfaces, or they can co-precipitate with or sorb to the surfaces of Fe- or Mn-hydroxides (11,12).

These changes in the geochemical form of the metals are very important, as they have a large influence their bioavailability to humans. Research on metal bioavailability in mine wastes has led to conflicting conclusions. *In vitro* assessments of bioavailability using sequential extractions and physiologically-based extraction tests and *in vivo* assessments in rats and rabbits have revealed that Pb salts such as Pb acetate, $PbSO_4$ and PbO generally are more bioavailable than PbS and Pb-containing mining ores (14,15,16). The relatively low bioavailability of metals in sulfides and mine ore have been cited as an explanation for the observation that children in mine-impacted areas have tended to have lower blood Pb than would be expected given the total Pb concentrations in their surroundings, especially compared to children in urban and smelter-impacted areas (17,18).

Relatively low bioavailability of metals in mining waste has also been shown for plant uptake of metals. Plants grown in mine-tailing amended soils take a smaller proportion of metals when compared to plants in control areas (19,20) with an effect that is most severe for the metals Cu and Pb and least severe for the metals Zn and Cd.

However, the usefulness of this information for predicting human exposure underplays the fact that secondary mineral phases (i.e., metal-containing minerals that have had been weathered, ingested, or otherwise transformed) can be substantially more bioavailable than primary minerals. A significant portion of Pb in mine wastes has been shown to be mobile in environmentally and biologically relevant solutions such as simulated gastric fluid (21). Furthermore, while many studies have focused solely on Pb, other metals (*e.g.*, Zn, Cd, Mn) that frequently occur in mine wastes can have greater environmental mobility than Pb and therefore also may pose more substantial health risks.

With regards to evidence in humans, several epidemiologic studies of communities exposed to lead-contaminated mining waste have failed to find evidence of a significant contribution

of mining waste exposure to elevations in blood lead levels amongst exposed children (22, 23,24,25,26,18).

On the other hand, a number of epidemiologic studies indicate that exposure to mining waste is a major risk factor for increased exposure to metals such as lead. Gulson et al. (27) used isotopic and microscopic characterization techniques to demonstrate that lead in soil samples from the Broken Hill lead mining community in Australia was a major source of lead in house dust and, in all likelihood, the blood samples of children, with 20% of the children having blood lead levels exceeding 20 μg/dL and 85% exceeding 10 μg/dL. Other investigators used multivariate regression analyses of blood lead levels to come to similar conclusions at other mining sites (28,29,30).

With respect to the TCSS, the U.S. Public Health Service's Indian Health Service informed the U.S. EPA in 1994 that 34% of the 192 Native American children tested from the Tar Creek area had blood lead levels exceeding 10 μg/dL; 15% had blood lead levels above 20 μg/dL (10). A blood lead survey subsequently conducted in the towns of Quapaw, Picher and Cardin in 1996 by the Oklahoma State Health Department (OSHD) found that the blood lead levels exceeded the U.S. Centers Disease Control's maximum recommended level of 10 μg/dL amongst 13.4% (9 of 67), 38.3% (31 of 81), and 63% (10 of 16) of the children tested, respectively (4). These findings contrast sharply with the statewide average blood lead concentration in children of 2 percent reported by the OSHD.

In 1997, baseline blood lead levels among Native American and White children 1–6 years of age residing in Ottawa County were measured as part of a community-based intervention study (known as the "Tribal Efforts Against Lead" [TEAL] Project) conducted by researchers at the University of Oklahoma and eight tribes of northeastern Oklahoma. The study area included the five towns constituting the Tar Creek Superfund site as well as Miami, the largest city in Ottawa County, and several other nearby small towns. Of the children tested, 21.4% lived in a former mining town. In a multivariate regression analysis, the investigators found that living in one of the former mining towns was associated with a 5.6 odds ratio (95% CI: 1.8–17.8) of having a blood lead >10 μg/dL even after adjusting for mean levels of lead in soil, floor dust, caregivers' education, and hand-to-mouth behaviors (31). Indices of lead paint (either exterior or interior) did not have a measurable impact on risk of elevated blood lead levels in this population.

A contributing factor in these exposures is that a significant quantity of chat has been dispersed in the community by its removal and use in dirt roads, as an aggregate in concrete, in building foundations, and for sandblasting and landscaping (32). In particular, there are concerns about the effects of children playing on the chat piles and mobilization of dust from the piles to adjacent residential areas. With respect to children's exposure, the issue of windborne transport may be particularly important. Studies have shown that metal concentrations in the fine particles available for windblown transport are enriched relative to the larger particles, with concentrations of Pb and Zn as high as 7,000 and 55,000 mg/kg, respectively (33). The highly elevated concentrations in this size fraction can be important for dust and soil routes of exposure. Soil and dust ingestion may be particularly important in children, for whom hand-to-mouth activity may be more common. Although there is evidence for limited bioavailability of metals in parent mine waste, exposure data suggest that the metals at the TCSS must have undergone transformations that make them more available for biological uptake. In order to develop proper interventions, it is thus imperative to better understand the underlying geochemical cycling that led to these potentially adverse exposures.

Finally, although the potential exists for residents at the TCSS to be also exposed to cadmium, manganese, and other metals, no biological sampling for metals other than lead has been conducted and published.

IV. Metal Mixtures and Kids: Toxicity

While previous neurodevelopmental research has focused extensively on lead (Pb) exposure, exposure to other environmental metals, such as arsenic (As) Cadmium (Cd) and manganese (Mn) may also have toxic effects that have not been well defined in human populations. Furthermore, concurrent exposure to *combinations* of metals, which is a better reflection of the "real world," may have synergistic neurotoxic effects. This situation is particularly critical for populations living near Superfund "mega-sites," as the majority of mega-sites have multiple contaminants. Former mining communities such as Bunker Hill, Idaho, Leadville CO, and Tar Creek, OK among others, are contaminated primarily with metals, including Pb, Cd, As, and Mn. The Tar Creek Superfund site is the focus of our team's Children's Environmental Health Center (CEHC) research project and the role of metal mixtures on child development is a predominant theme.

Early Life Programming of Neurodevelopment

Why are children most vulnerable to neurotoxins? During fetal life and early childhood, neurons must undertake migration, synaptogenesis, selective cell loss, myelination and a process of selective synaptic pruning before development is complete (34). Even minor inhibitory or excitatory signals imposed by environmental toxicants at early stages of CNS development can therefore cause alterations to subsequent processes. The nature of CNS development limits the capacity of the developing brain to compensate for cell loss or disruptions in neural networking caused by neurotoxic chemicals and can lead to reductions in cell numbers(35) or alterations in synaptic architecture (36). Neurotransmission during the prenatal/early childhood period is a signaling process which determines synaptic and neuronal pruning (37). Lead interferes with this process by both inhibiting depolarization by blocking Ca++ channels and by stimulating neurotransmitter release in the absence of an environmental cue (38–42). Moreover, lead, cadmium, arsenic and manganese have all been demonstrated to inhibit depolarization-evoked neurotransmitter release. This effect has even been shown to be synergistic when these metals are administered as a mixture (43). By either inhibiting signal transmission or producing spontaneous depolarization in the absence of environmental stimuli, the effect of toxic metals may be to add noise to the neuronal signaling processes which determine synaptic pruning and synaptogenesis. The effects of metals on synaptogenesis and pruning may be the key to understanding why children are more sensitive to neurotoxins than adults, in whom synaptic architecture is more static and less plastic.

Neurotoxicity of Arsenic

Arsenic has been traditionally categorized as a *peripheral* neurotoxin, producing a clinical picture of severe polyneuropathy. However, recent animal studies suggest that this neurotoxicity includes the *central nervous system* as well. Rodriquez VM et. al, (44) demonstrated learning and behavioral deficits in rats exposed to oral arsenic prenatally in maternal drinking water. Arsenic exposed offspring showed increased spontaneous locomotor activity and increased errors in delayed alternation tasks (a test of memory) compared to unexposed controls. In addition, Nagaraja et. al. (45) demonstrated delayed acquisition and extinction of operant behaviors following arsenate exposure in drinking water. Mechanistically, these deficits may be due to increased oxidative toxicity and changes in neurotransmission. Rao & Avani (46) and Chaudhuri et. al. (47) demonstrated increased neurotoxic oxidative stress in mouse brains following oral administration of arsenic trioxide. Other investigators have demonstrated changes in neurotransmitter levels, such as

acetylcholine, dopamine, serotonin and norepinephrine in the CNS following As exposure (36,48,49). Chattopadhyay et. al. (50) found that arsenic exposure altered neural networking and led to an increase in reactive oxygen intermediates. The same research team demonstrated that among As exposed rats during pregnancy, fetal brain neurons underwent apoptotic changes and neuronal necrosis (48). Recent epidemiologic literature also confirms that *environmental* levels of arsenic exposure may produce neurocognitive deficits in children (51). Calderon J et al. (52) demonstrated that urinary As levels inversely predicted verbal IQ among 39 children living proximal to a smelter, even after adjusting for blood lead. Recently, Wasserman et al. (53) conducted a cohort study of children which demonstrated a strong adverse effect of elevated drinking water As levels on IQ after adjusting for covariates.

Neurotoxicity of Manganese

Unlike Arsenic and lead, manganese is not only a toxic metal but is also an essential nutrient (54). Nutritional deficiencies of manganese, therefore, are possible but extremely rare. Adult workers exposed to high levels of air Mn levels have memory loss, anxiety, behavior changes, and sleep disturbances (55–57). In its final stages, manganism leads to a Parkinsonian-like syndrome. The primary mechanisms of manganese neurotoxicity are not well understood, but appear to involve increased oxidative damage to neuronal cells (58–60). With respect to potential developmental neurotoxicity, Tran et al. (61) demonstrated that increased dietary Mn supplements fed to lactating dams was associated with decreased striatal dopamine levels one month following cessation of supplements as well as significant increases in passive avoidance errors among animals who received Mn (62). In adults living in Greece, abnormal neurological scores were associated with higher hair and water manganese concentrations (63). Santos-Burgoa et al. (64) reported a significant inverse association between blood Mn levels and Mini-Mental Status Exam scores among adults living proximal to a Mn mining district in central Mexico. In Chinese children, exposure to elevated manganese concentrations in drinking water was associated with lower scores on tests of short-term memory, manual dexterity, and visual-perceptual speed (65). We recently reported a child with manganism (blood Mn 3.8 μg/dL) from a private well water source with normal full scale IQ but deficits in verbal, visual and general memory indices (66). Using the McCarthy General Cognitive Index test at age 5 years, Takser et al. (67) reported deficits in memory, attention and psychomotor indices associated with elevated umbilical cord Mn levels. More recently, Wasserman et al. found inverse associations between water Mn levels and IQ among ten year old children.

Neurotoxicity of Cadmium

Like As and Mn, Cd has neurotoxic properties, but population based studies in children are lacking, although some research has been reported. The neurotoxicity of cadmium in children was investigated in several studies in the 1970s and 1980s but has received little attention since. In most of these studies, the biomarker of exposure was the concentration of cadmium in hair. In case-control studies in which the hair concentration of cadmium of a clinically-defined group was compared to that of a reference group, higher concentrations were reported in mentally retarded children (68,69) and in children with learning difficulties or dyslexia (70,71), but not in children with autism (72,73) or in children with any of several neuropsychiatric diagnoses (motor, perceptual, speech, or attention disorders) (74). In cohort studies, Thatcher et al. (75, 76) reported that the concentration of cadmium in hair was significantly inversely related to adjusted IQ scores, particularly verbal IQ, and to visual evoked potentials; (77) and Marlowe and colleagues (78,79) reported associations between increased hair cadmium and children's performance on visual-motor tasks. Marlowe et al. (80) also reported that lead and cadmium acted synergistically in impair children's classroom behavior.

The Neurotoxicity of Lead

The literature supporting the neurodevelopmental toxicity of lead is extensive and a comprehensive summary is beyond the scope of this paper. While controversy still exists regarding the levels at which lead toxicity manifests clinically, there is widespread acceptance that lead is neurotoxic. Lead exposure can occur pre and post-natally, because lead freely crosses the placenta (81). Levels of lead circulating in maternal blood provide information about in-utero exposure to the fetus (82). Several investigators have reported inverse associations between infants' scores on tests of cognitive and motor development and an index of fetal lead exposure such as umbilical cord blood concentration (83,84) or maternal blood lead during pregnancy (85). Neonatal (10-day) blood lead levels, interpreted as an index of prenatal exposures, were associated with worse performance at age 4 years on all scales of the Kaufman-Assessment Battery for Children (K-ABC) (86). Bellinger et al. (87) demonstrated that the deficits of children with higher prenatal exposures (cord-blood lead levels of 10 to 25 μg/dL) persisted until 2 years of age, despite postnatal exposures that were comparable to those of children with lower prenatal exposures. The toxicity of lead in combination with other metals, particularly in humans, is largely unexplored.

Metal mixtures and Neurodevelopment

Data on chemical mixtures in humans are limited only to a few studies (88–90). Animal studies have demonstrated increased spontaneous motor activity among rats with joint Mn/Pb exposures relative to those with only one metal (91) [52][e2]. In studies of conditioned avoidance responses, lead plus manganese decreased learning more than either lead or manganese alone (91). Gestational exposure to lead and Mn combined will reduce birth weight and *brain weight* greater than either metal alone (92). Co-administration of Pb and Mn has been demonstrated to increase brain lead levels approximately 3 fold (91,93). Similar to joint Mn and Pb exposure, rats jointly exposed to As and Pb will have higher levels of Pb in the midbrain and hippocampus than animals exposed to lead alone (94). In addition, multiplicatively greater changes in monoaminergic neurotransmitter levels occur in the brains of rats exposed to lead and arsenic jointly than for either metal alone (94). Rodriguez VM et al. (44) administered *mining waste* containing Pb, Mn and As to rats in their diets and found elevations in both As and Mn in rat brains relative to controls with single metal exposures. The 3 metal concentrations were highly correlated and predicted decreases in dopaminergic neurotransmitter release following depolarization.

Recently, we conducted a study of As/Mn exposure and IQ among sixth grade children living in the Tar Creek Superfund site (95). Hair metal levels were used as an index of exposure. An inverse association existed for verbal and full scale IQ with hair As and hair Mn (plot of[e3] verbal IQ vs. hair Mn. In linear regression models both hair As and hair Mn were significantly associated with both full scale and verbal IQ. Hair Pb and hair Cd did not significantly predict any IQ test score. The effect of both hair As and hair Mn remained after adjusting for maternal education and gender as well. Hair As and Mn were highly correlated (r squared =0.42) and could not be entered into a single model due to co-linearity. However, there was evidence of an interaction. When the data were dichotomized by the median values of hair As and hair Mn, Only subjects who jointly had elevated hair As and Mn had lowered IQ test scores, suggesting that joint exposures may be most toxic.

V. Metal Mixtures: Potential Interventions

Nutrition and Toxic Metals

There is substantial variability in biomarkers of internal dose among children exposed to metals. Multiple factors contribute to this variance. Behavioral factors such as hand to mouth activity, differences in environmental levels even among children living in the same

neighborhood, size differences in children of the same age, and variability in genetic susceptibility all likely play a role. Many of these factors cannot be modified or are difficult to measure limiting their clinical utility for pediatricians caring for high risk children. One of the few factors which can be modified clinically is diet. A substantial body of evidence has demonstrated that body stores of essential nutrients, such as calcium, zinc and iron are generally inversely related to the absorption of toxic divalent metals such as Pb, Mn and Cd.

Calcium and Toxic Metal Absorption

Calcium influences not only the remobilization of lead from bone but also the absorption of lead in the gut. Animals fed a calcium-deficient diet are found to have higher blood lead levels than control animals with identical lead exposures through water(96,97). The inverse association between dietary calcium intake and blood lead concentrations has also been demonstrated in large cohort studies, such as the National Health And Nutrition Examination Study (98) and even in early experimental studies (99,100). This large body of evidence eventually led to a randomized controlled trial of calcium supplementation in the formula of infants to prevent lead poisoning (101). While the study did not demonstrate a significant effect in preventing lead poisoning, the sample size was relatively small (103 infants total), and calcium supplementation was discontinued at one year of age and not continued to the peak age of lead poisoning(1.5–3 years of age). Our own research group has demonstrated that calcium supplementation will decrease lead exposure during lactation (102). Calcium absorption is also inversely associated with other divalent metals such as cadmium and manganese which may be transferred in breast milk and are found in bone (103–105). Low dietary calcium intake has been associated with increased manganese absorption. Yasui et al. (106) found a significant increase in bone concentrations of manganese when rats were fed a low calcium diet. Similarly, Murphy et al. (107) found a 4 fold increase in serum manganese concentrations in rats fed a low-calcium, normal-manganese diet. Cadmium absorption is also inversely associated with dietary calcium (108,109). In addition, low dietary calcium alters the tissue distribution of cadmium increasing brain levels (110). A low calcium diet coupled with cadmium exposure increased bone demineralization during pregnancy and lactation (111). Sari et. al., studied the effect of calcium supplementation in suckling rats through gavage supplementation of breast milk with cow's milk and found reductions in body Cd (112). Walter et al. (113) found a similar effect of calcium supplements reducing cadmium retention in rats.

Iron and Toxic Metals Absorption

In addition to inverse associations between dietary calcium intake and absorption of lead, manganese, and cadmium, there is substantial evidence that iron deficiency upregulates the absorption of these same three metals as well. During iron deficiency, regulatory mechanisms cause an increase in the percentage of ingested iron that is absorbed (96). Barton suggested that the effects of iron deficiency on lead absorption are mediated through a common absorptive pathway for both metals (114). In clinical studies, an inverse association between dietary iron and blood lead was found by Hammad in urban Baltimore children (115). Similarly, our research group recently found an association between iron deficiency and low-level lead poisoning in children (116,117). Other clinical studies have also demonstrated that high body iron stores are associated with decreased blood lead levels (82,118). Iron deficiency will also upregulate manganese absorption (119). Intracellular uptake of manganese occurs with co-transport of iron (59). Animal studies clearly demonstrate that iron deficiency will increase manganese absorption independent of body manganese stores (119,120). Similarly, an inverse association between serum ferritin levels and manganese absorption has been demonstrated in humans (121). Body iron status also appears to modify cadmium absorption. Groten et al. showed that low dietary iron content was associated with increased intestinal uptake of cadmium in rats (122). Increases in dietary cadmium absorption have been demonstrated to be inversely associated with serum ferritin levels in both mice and humans (123–125).

Selenium and Arsenic

As metabolism and toxicity are more closely related to a different essential mineral-Selenium. Selenium (Se) is an essential trace element involved in antioxidant defense, as well as thyroid function and immune function. While clinically-apparent Se-deficiency diseases have been reported, evidence is emerging that pre-clinical deficiency can also cause adverse health effects. Available data indicate that Se antagonizes arsenic-induced disease. The proposed mechanisms of this interaction include the increase of biliary excretion and direct interaction/precipitation of selenium and arsenic, and their effects on zinc finger protein function, cellular signaling and methylation pathways (126). Maintaining body stores of selenium may be critical in preventing the neurotoxicity of As.

Other Interventions

The above section highlights the potential benefits of nutrient supplementation in preventing the absorption of toxic metals. Other interventions include chelation for lead poisoned children and environmental hazard reductions. Chelation for low level lead poisoning (blood leads less than 40 μg/dL) has not been demonstrated to be effective in preventing poorer cognitive outcomes (127). Prevention measures have therefore become the focus of most clinical efforts, but such measures have been largely unsuccessful when tested as randomized controlled trials. (101). Attempts to reduce dust loading in the housing of high risk children have been similarly disappointing. A systematic review of randomized, controlled trials of low-cost, dust control interventions to determine the effect of lead hazard control on children's blood lead concentration found no significant differences in mean change in blood lead concentration for children by group assignment (128). A randomized trial of soil abatement in urban children conducted in the late 1980's and early 1990's also did not find a significant effect on children's blood lead levels (129). With respect to soil abatement at Superfund sites in which lead paint may be a less dominant source, there are no randomized trials similar to Weitzman et al. However, Lanphear et al. (130) did find a significant decrease in blood lead levels associated with soil abatement in an observational study conducted in a population adjacent to a lead/arsenic smelter. Given the ethical ramifications of a nontreatment arm and the inability to blind soil abatement measures, a true randomized controlled trial of soil abatement within a Superfund Mining Megasite is unlikely to be conducted. The weight of the existing evidence would therefore suggest that soil abatement is beneficial at such sites.

Given that few studies have demonstrated effective measures that reduce blood lead levels, removing lead from a child's environment is likely the most effective public health measures. However, clinicians are most often faced with individual children who are either lead poisoned or in a known high risk environment. Measures to reduce dust exposure- such as focused cleaning around window sills and door mats to minimize dust lead loading should be encouraged. While more costly, ideally a household should use a vacuum equipped with a high-efficiency particulate air (HEPA) filter otherwise there is risk of spreading the dust beyond the area of cleaning. Cleaning should involve vacuuming of major horizontal surfaces (floors, windowsills, and furniture) as well as mopping. Hand washing, particularly after outdoor play should be emphasized. Dust and soil are likely sources of not just lead, but of multiple metals in children living near former mining communities, Furthermore, nutritional interventions aimed at preventing lead absorption likely will prevent the absorption/toxicity of other toxic metals, such as Mn, Cd, and possibly As. Nutritional interventions have the added benefit of reducing the overall prevalence of iron deficiency anemia or calcium deficiency, which may have their own neurotoxic effects. Nutritional supplements of iron, zinc and calcium may therefore work both directly and indirectly to improve neurodevelopmental outcomes in at risk children and should be encouraged by clinicians.

V. Metal Mixtures: Summary and Lessons for Clinicians

In summary, much is known about the toxicity of individual environmental risk factors, but little is known about their potential interactions in mixtures—which, unfortunately, represents the vast majority of exposures stemming from "real world" hazards such as toxic waste sites. In this paper, we have used the case study of the Tar Creek Superfund site (TCSS), the focus of the authors' research and an area where thousands of residents, including children, live amidst mounds of "chat" mining waste, to discuss and illustrate the challenge assessing and controlling risks from mixtures of toxic metals. An issue that must first be evaluated is the various routes of exposure and "bioavailability" (ability of metals to be absorbed) once mining waste dusts are ingested or inhaled. The evidence that such exposures are occurring at the TCSS with resulting doses of lead and other metals is high, although the extent remains to be clarified. The neurotoxicity of lead at low levels is now well-established, and neurotoxicity to children of low-level exposures to arsenic, manganese, and other metals is of great concern and the subject of on-going research. Animal studies and preliminary human studies suggest that synergy (metal-metal interactions that multiply risk) may also occur.

While this research progresses, there are some low-risk high-potential-benefit interventions that make particular sense for communities exposed to mixtures of metals (such as mining waste), namely, focused cleaning of surfaces with a high efficiency particulate air vacuum cleaner, frequent hand-washing and nutritional supplementation (by foods and/or supplements) containing iron, zinc, calcium, and possibly selenium.

When confronted by patients or communities that are potentially affected by hazards such as metal mixtures in mining waste, clinicians need to be able to access and interpret a diverse array of informational sources on exposures, potential toxicity, methods of environmental and medical monitoring, and best practices. A growing amount of such information is becoming available on websites maintained by government, non-governmental organizations, and academic institutions (see Table 1 for a list of suggested internet resources related to toxic wastes and health). The availability of the internet and the growing sophistication of search engines make such information more easily available than ever before, but integrating and synthesizing the information to arrive at specific clinical recommendations can be challenging, even for clinicians trained in environmental health and environmental medicine, and particularly in a setting, as prevails with respect to mixtures, in which many unknowns exist..

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Table 1

Examples of Internet-based Resources Related to Toxic Metals, Wastes and Health

Description	Website
ATSDR (Agency for Toxic Substances and Disease Registry)—Government agency that studies health effects of toxic waste	http://www.atsdr.cdc.gov
ATSDR Case Studies in Environmental Medicine (Information for clinicians on specific exposures)	http://www.atsdr.cdc.gov/HEC/CSEM/csem.html
ATSDR Chemical Mixtures Program	http://www.atsdr.cdc.gov/mixtures.html
Center for Children's Environmental Health and Disease Prevention Research at the Harvard School of Public Health (Metal Mixtures and Children's Health)	http://www.hsph.harvard.edu/niehs/children
Dartmouth Toxic Metals Research Program	http://www.dartmouth.edu/~toxmetal/HM.shtml
EPA Superfund Program (general description)	http://www.epa.gov/superfund
EPA Search Engine (for finding toxic waste sites in your community)	http://cfpub.epa.gov/supercpad/cursites/srchsites.cfm
Metals Epidemiology Research Group (a Harvard-University of Michigan research collaboration on metals toxicity)	http://www.hsph.harvard.edu/merg
NCEH (National Center for Environmental Health)—Government agency that addresses broad environmental health issues	http://www.cdc.gov/nceh