REFLECTIONS ON HEXAVALENT CHROMIUM: HEALTH HAZARDS OF AN INDUSTRIAL HEAVYWEIGHT

CI61Q/CI71M Principios de Remediación y Restauración

Profesores C. Espinoza y M.P. Mena

Semestre Primavera 2007

Environmental Health Perspectives V.108, N.9, Sep00

It's been 80 years since it was first noticed that workers in the German chrome ore industry developed lung cancer more often than the rest of the population. Study after study since the 1920s has shown that people who work around industrial processes using chromium have higher-than-normal rates of lung and nasal cancers. U.S. industry has used chromium commercially for more than 100 years, and today chromium is a primary contaminant at over half of all Superfund hazardous waste sites. But despite a century of industrial use, there are still holes in the basic knowledge about how chromium affects major organ systems in animals and humans, as well as the risks associated with various pathways of exposure.

Chromium occurs mainly in three forms. Metallic chromium (Cr[0]) is a steel-gray solid with a high melting point that's used to make steel and other alloys. Chromium metal does not occur naturally; it is produced from chrome ore. Trivalent chromium (Cr[III]) occurs naturally in rocks, soil, plants, animals, and volcanic emissions. This form is believed by many to play a nutritional or pharmaceutical role in the body, but its mechanism of action is unknown. Cr(III) is used industrially as a brick lining for high-temperature industrial furnaces and to make metals, metal alloys, and chemical compounds. Hexavalent chromium (Cr[VI]) is produced industrially when Cr(III) is heated in the presence of mineral bases and atmospheric oxygen (for instance, during metal finishing processes). It is this third form of chromium that has proven to be of the greatest occupational and environmental health concern.

Cr(VI) in the Body

Cr(VI) can enter the body when people breathe air, eat food, or drink water containing it. Cr(VI) is also found in house dust and soil, which can be ingested or inhaled. Of the various forms of chromium, Cr(VI) is the most toxic.

Certain Cr(VI) compounds have been found to be carcinogenic in humans, but the evidence to date indicates that the carcinogenicity is site-specific--limited to the lung and sinonasal cavity--and dependent on high exposures, such as might be encountered in an industrial setting. Cr(VI) can cause a wide range of other health effects. Inhaling relatively high concentrations of some forms of Cr(VI) can cause a runny nose, sneezing, itching, nosebleeds, ulcers, and holes in the nasal septum. Short-term high-level inhalational exposure can cause adverse effects at the contact site, including ulcers, irritation of the nasal mucosa, and holes in the nasal septum. Ingestion of very high doses of Cr(VI) can cause kidney and liver damage, nausea, irritation of the gastrointestinal tract, stomach ulcers, convulsions, and death. Dermal exposures may cause skin ulcers or allergic reactions (Cr[VI] is one of the most highly allergenic metals, second only to nickel). And studies of mice fed high doses of Cr(VI) have shown reproductive effects including reduced litter size and decreased fetal weight.

There is a great deal of controversy about the relative health effects of the various routes of exposure for Cr(VI). According to the International Agency for Research on Cancer (IARC), ingested Cr(VI) is largely converted to Cr(III) in the stomach, a fact that many chromium experts

believe prevents ingestional exposures from posing significant health dangers, since Cr(III) is not readily absorbed into the body. The saliva, gastric juice, intestinal bacteria, blood, liver, epithelial lining fluid, pulmonary alveolar macrophages, peripheral lung parynchema, and bronchial tree have all been associated with eliminating Cr(VI) from the body. In an article published in the March 1997 issue of *Carcinogenesis*, Silvio De Flora, director of the Department of Health Sciences at the University of Genoa, and colleagues present estimates of the ability of various human organs, cell populations, and fluids to reduce Cr(VI) in the body. They found that major detoxification is accomplished by red blood cells, with over half of a 100-microgram (µg) dose of Cr(VI) being sequestered or reduced by 1 milliliter of blood within 60 minutes. De Flora and colleagues write, "The massive reducing and sequestering capacity of the blood explains why [Cr(VI)] exerts its toxicological consequences at the portal of entry into the organism, while it is not a systemic toxicant or carcinogen."

Other experts are not convinced. In a review article on the toxicity and carcinogenicity of Cr(VI) in animals and humans that was published in the September 1997 issue of *Critical Reviews in Toxicology*, Max Costa, chairman of the Department of Environmental Medicine at the New York University Medical Center, cites studies that have found that as much as 10% of Cr(VI) is absorbed following oral exposure in humans. He also references studies of occupationally exposed subjects since the early 1980s that estimated that 10% of absorbed Cr(VI) may remain in the human body for up to 5 years. Finally, Costa points to research he and colleagues published in the March 1993 issue of *Biological Trace Element Research*, which demonstrates that total chromium accumulated in the liver, kidney, spleen, bone, lung, heart, muscle, and blood of rats and mice dosed orally with Cr(VI) for 4 or 8 weeks. In his review Costa concludes, "The presence of [chromium] in these tissues indicates a potential for toxicity and cancer in many different tissues following drinking water exposure to [Cr(VI)] in solution." (This opinion is highly controversial, however, and in a commentary published in the April 2000 issue of *Carcinogenesis*, De Flora contends, among other criticisms, that several of the studies cited in Costa's paper reflect an extremely heterogeneous range of possible exposures, some of which included agents other than chromium.)

Because of structural similarity to phosphate, which is transported into all types of cells, if Cr(VI) does reach a cell, it can enter it. Once Cr(VI) enters the cell, it is chemically transformed to the more stable Cr(III). This does not mean, however, that the cell is necessarily safe from adverse effects. One of the major reasons Cr(III) does not cause toxic effects is that, unlike Cr(VI), it has a poor ability to enter cells. However, inside the cell Cr(III) has the capacity to damage DNA. Two decades' worth of research by the late Karen Wetterhahn, a chemist at Dartmouth Medical School in Hanover, New Hampshire, and De Flora on the uptake and reduction of Cr(VI) by cells indicates that Cr(VI) acts as a "Trojan horse" for delivering DNA-damaging Cr(III) into cells.

The process by which Cr(VI) is reduced to Cr(III) can cause many forms of DNA damage: oxidative DNA lesions such as strand breaks, chromium-DNA adducts, DNA-DNA interstrand cross-links, and DNA-protein cross-links. (An adduct is a modification of a biological molecule--in this case, DNA--caused by the covalent attachment of a chemical, such as chromium; cross-links are a specific class of adduct.) Research by Steven Patierno, a professor of pharmacology and genetics and of environmental occupational health at The George Washington University in Washington, D.C., and colleagues first identified a potential mechanism of genotoxicity for intracellular Cr(III). Those studies, published in the March 1994 issue of *Molecular Carcinogenesis* and the November 1994 and July 1996 issues of *Carcinogenesis*, indicate that Cr(III)-induced DNA-DNA interstrand cross-links are the lesions responsible for blocking DNA replication.

Recent work by Costa and colleagues looked at the possible mutagenicity of certain Cr(III)-induced DNA adducts. In an article published in the 15 April 1998 issue of *Nucleic Acids Research*, the scientists found that Cr(III)-glutathione cross-links exhibited the greatest mutagenicity of the adducts studied, with a mutation frequency five times greater than background. This observed mutagenicity complements other studies on Cr(III)-dependent DNA lesions, which demonstrate the importance of a Cr(III)-dependent pathway in Cr(VI) carcinogenicity. Additional studies are investigating the relative importance of oxidative and Cr(III) pathways in genetic damage caused by exposure to Cr(VI).

Cr(VI) in the Environment

Cr(VI) compounds are emitted into the air, water, and soil by a number of different industries. In the air, chromium compounds are present mainly as fine dust particles that eventually settle over the land and water.

The *Report on Carcinogens*, published by the National Toxicology Program, says the atmospheric total chromium concentration in U.S. air is typically less than 0.01 µg per cubic meter (m^3) in rural areas and 0.01-0.03 µg/m^3 in urban areas. Chromium in ambient air is not regulated.

The *Report on Carcinogens* also indicates that typical tap water can contain 0.4-8.0 µg per liter (L) total chromium, and that chromium in rivers and lakes usually falls between 1 and 10 µg/L. Cr(VI) by itself is not regulated in drinking water. The U.S. Environmental Protection Agency (EPA) regulates only total chromium in drinking water and has set a maximum contaminant level of 100 µg/L (more stringent state limits are often set at half that amount).

Soil, meanwhile, contains on average 400 parts per million total chromium, but this depends on the balance of oxidizing and reducing agents in the soil. Chromium can change valence state in soil and sediments depending upon the local physical, chemical, and biological conditions. For instance, says Paul Lioy, deputy director of the Environmental and Occupational Health Sciences Institute in Piscataway, New Jersey, in soils with a high pH, Cr(III) can convert to Cr(VI). According to the EPA's 1998 *Toxicological Review of Hexavalent Chromium*, Cr(VI) found in the soil is generally converted to Cr(III) by organic matter. Soil concentrations are not strictly regulated by the EPA, but rather are subject to soil screening levels. These levels are devised on a site-by-site basis according to the pathways present at the site (for example, whether people are likely to handle the soil) and certain site characteristics (for example, whether the soil is loamy or sandy) to determine whether investigation or cleanup is warranted.

The Occupational Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health (NIOSH) establish permissible exposure limits (PELs) and recommended exposure limits (RELs), respectively, for hazardous substances in the workplace. PELs are based on the feasibility of controlling the exposure in question within the workplace, while RELs are based on requirements for preventing occupational disease. Although employers are legally bound only by PELs, they are encouraged by NIOSH to follow whichever limit is the more protective. The PEL for Cr(VI) in workplace air during an 8-hour work day, 40-hour work week is 100 µg/m^3, while the REL for carcinogenic Cr(VI) compounds in workplace air is much lower: only 1 µg/m^3.

It has been estimated that workers in some 80 different professional categories may be exposed to Cr(VI). Various Cr(VI) compounds are used in leather tanning, the production of textiles, dyes, and pigments, and chrome plating. Other sources of chromium emissions include oil and coal

combustion, stainless steel welding, steel production, cement plants, industrial paint and coating manufacture, and cooling towers, which use Cr(VI) as a rust inhibitor for their submerged moving parts.

Occupational exposures to Cr(VI) compounds can be quite acute. Although breathing in Cr(VI) at concentrations as low as 2 µg/m^3 can cause sneezing and irritation of the nasal mucosa, air concentrations of Cr(VI) compounds can get much higher than that in certain workplace settings. In chrome plating workshops with local exhaust, for example, concentrations generally range from 10 to 30 µg/m^3; in shops without local exhaust, concentrations can climb to 120 µg/m^3. Arc, stainless steel, and alloy steel welding can produce even higher concentrations; according to IARC, depending on the process, welding fumes have been found to contain concentrations as high as 1,500 µg/m^3.

The alchemy of contamination. Chromium in the soil of this New Jersey industrial parking lot has dissolved in a pool of standing water. Because chromium can go into solution and move through soil, chromium pools and blooms (the crystallized chromium left on the surface when the water evaporates) may occur some distance from the original site of contamination.

NIOSH and the Agency for Toxic Substances and Disease Registry (ATSDR) have determined that home-based toxic exposures can happen when people who work in certain industries go home at night, in what are known as worker-to-family exposures. Family members may be exposed to Cr(VI) and other hazardous materials through contact with contaminated clothes, shoes, and other items.

Home exposures can also come from living near hazardous waste sites. A study published in the December 1998 issue of *EHP* by Alan H. Stern, chief of the Bureau of Risk Analysis within the New Jersey Department of Environmental Protection, along with Lioy and colleagues examined the relationship between chromium in household dust and chromium in the urine of residents of Hudson County, New Jersey, which for 70 years was home to three major producers of the Cr(VI) compound chromate. Over their lifetime, the sites produced some two million tons of chromium-contaminated slag, which was used as clean fill on local residential and commercial construction sites. In some parts of the county, the researchers measured soil concentrations of toxic Cr(VI) as high as several hundred parts per million. The researchers did not report any health effects among the people they studied, but their findings show that, especially for children, the presence of chromium in household dust correlates with urine chromium in a

continuous fashion. Such an effect was not present in people who did not live near the chromate production waste sites. Says Lioy, "Our research . . . demonstrated that chromium can be easily transported into the residential house dust from outdoor sources." The researchers found that once the chromium-contaminated residential soil was removed, the chromium concentrations in the homes were reduced over time to background levels.

Chromium can be measured in the urine, serum, red blood cells, and whole blood, while skin patch tests may indicate allergies to chromium. The most common approach to biomonitoring human exposure to toxic metals is determining their concentrations in blood and urine.

The problem with using this approach with Cr(VI) exposure is the ubiquitous presence of nontoxic Cr(III) in food and dietary supplements. Because Cr(VI) can convert to Cr(III), chromium concentrations in bodily fluids could be influenced either by exposure to Cr(VI) or by more benign exposures such as eating chromium-rich food.

However, says Stern, with proper data collection and statistical analysis to control for potential dietary sources of total chromium exposure as well as other potential determinants of chromium biomarker concentration, statistically significant differences in chromium biomarker levels between exposed and control populations can provide strong evidence of exposure to environmental chromium, including Cr(VI). In industrial situations with high and well-documented Cr(VI) exposure, it is generally not a problem if dietary chromium adds to blood concentrations. Industrial Cr(VI) exposures can create such high blood and tissue concentrations in people that the relatively low amount of Cr(III) that most people take in through environmental exposures is insignificant in comparison, and wouldn't affect the ultimate diagnosis of toxic levels of exposure.

Industry Efforts

Various industry sectors are addressing the health risks posed to workers and the environment by Cr(VI) as well as other toxic compounds. The American Chemistry Council (ACC; formerly the Chemical Manufacturers Association), which represents members on public policy issues and coordinates industry research and testing programs, launched its Responsible Care initiative in 1988 to address public concerns about chemical manufacture and use. The initiative offers a set of operating principles to help participants manage chemical production and handling more responsibly in order to prevent on-the-job accidents, injuries, spills, and environmental damage.

The High Production Volume (HPV) Chemical Challenge was designed by the EPA, the ACC, and the Environmental Defense Fund as a means of securing hazard-screening data for more than 2,800 of the highest-volume U.S. industrial chemicals (those made or imported at more than one million pounds per year), including several chromium compounds. Chemical producers and importers who agree to the voluntary challenge will provide basic toxicity data on the HPV chemicals they work with, with a 2004 deadline to complete testing for all HPV chemicals. The collaborative effort will allow the toxicity data gaps associated with HPV chemicals to be filled more quickly than the EPA could do on its own.

In the paint and coating industry, federal regulations strictly limit the use of lead chromate pigments--which give traffic markings their distinctive yellow color--to industrial products like traffic paints, finishes for machinery, and equipment and metal primers, says Steve Sides, vice president of environmental health and international affairs for the National Paint and Coatings Association, a Washington, D.C.-based trade organization. In fact, he says, these pigments are banned for use in consumer paints or on goods manufactured for potential use by or around

children. "OSHA regulations limit workplace exposure to hexavalent chromium," he adds, "and that's had a limiting effect on their use."

According to Sides, industrial coatings manufacturers have moved away from Cr(VI)-containing products to help customers meet compliance obligations. "For the last six years," he says, "the state of Minnesota has strictly regulated all coatings products containing heavy metals, including lead, mercury, cadmium, and hexavalent chromium--a regulation the paint industry has supported." Sides says many state and federal specifications for coatings, including those issued by the Department of Defense and the General Services Administration, still allow the use of Cr(VI), but planned revisions to the government specification system may finally change this scenario.

To solicit industry input in conducting research and setting environmental policy, the EPA implemented the Common Sense Initiative (CSI) in 1995 for six pilot industrial sectors: automobile manufacturing, computers and electronics, iron and steel work, printing, metal finishing, and petroleum refining. Instead of addressing environmental pollution by medium--by implementing broad regulations for air or water emissions--the initiative addresses problems by industrial sector. This means that when new regulations are established, they are more responsive to both the needs and the particular risks of a specific industry. As the EPA states in its 1998 report *Characterizing Risk at Metal Finishing Facilities*, "Reduced emissions do not necessarily equate to a proportional reduction of health risks. . . . [R]educing emissions where there is little or no exposure would yield a smaller health benefit relative to reducing emissions where there is much potential exposure. With regards to toxicity, a large decrease in the emission of a chemical of relatively low toxicity may have a smaller health benefit than a small decrease in a more toxic compound."

Under the CSI, subcommittees for each industrial sector investigate ways to create sector-specific alternatives to the current regulatory system in the areas of pollution prevention, reporting, compliance, permitting, and environmental technology. By creating a new regulatory system that is customized to the specific needs and problems of a particular industry, the EPA hopes to encourage innovation and spur facilities to meet or exceed legal requirements. The *Characterizing Risk* report remarks that EPA rule making has often resulted in litigation, drawing resources away from protecting the environment toward protecting the legislation, and says, "The EPA hopes CSI will provide a forum within which former adversaries will become partners in protecting the environment."

In 1997, the CSI Metal Finishing Subcommittee published an environmental research and development plan that sets forth eight priority research needs as identified by metal-finishing sector stakeholders themselves. Among the research needs are the development and application of simple methods to assess and quantify the emissions from plating operations, and the use of these values to characterize risks to workers, surrounding communities, and the environment. The plan also calls for the continuation and expansion of research and development on various aspects of reducing and eliminating air, water, and soil emissions from chrome plating operations.

Additional Research Needs

As the main federal statute for identifying and remediating uncontrolled hazardous waste sites, the 1980 Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA, or Superfund) directs the ATSDR to initiate research to fill key data gaps for the 30 most toxic hazardous substances found in Superfund sites, a list that includes chromium. In a 1997 report

titled *The Toxicologic Hazard of Superfund Hazardous Waste Sites*, which examined toxicity data for these 30 substances, the ATSDR identified the following research needs for chromium: dose-response data in animals for acute-duration exposure to Cr(VI) and Cr(III) via oral exposure and for intermediate-duration exposure to Cr(VI) via oral exposure, a multigeneration study of reproductive toxicity via oral exposure to Cr(III) and Cr(VI), an immunotoxicology battery of tests following oral exposure to Cr(III) and Cr(VI), and a two-species study of developmental toxicity via oral exposure to Cr(III) and Cr(VI).

Lioy adds that biomarkers for different forms of chromium need to be validated before use in human studies. He also says that the levels of chromium forms need to be detected in various media that are associated with various routes of exposure, and that applications of biomarkers must be coupled to physical or chemical markers of exposures and validated for use in situations that assess environmental health. The report concludes that immunotoxicity data are lacking for most of these top 30 substances (including chromium), and calls this "a serious deficiency in knowledge needed by health and risk assessors because of the essential role of the immune system for protecting one's health." The report also notes the paucity of research on the dermal effects of Cr(VI).

In the ATSDR's draft *Environmental Public Health Research Agenda, 2002-2010*, intended as a means of guiding research supported by the agency over the next decade, the ATSDR addresses the issue of worker-to-family exposures, which it says may contribute substantially to total exposures to hazardous substances in the environment. The draft agenda cites three goals regarding worker-to-family exposures: identify occupational practices associated with worker-to-family exposures, determine the contribution of worker-to-family exposure to total hazardous environmental exposures and the occurrence of adverse health outcomes, and develop and evaluate interventions to prevent such exposures. Suggested research approaches include reviewing existing databases to identify possible worker-to-family exposure scenarios and developing health education materials to educate workers about the risks of carrying contaminants home.

After a century of widespread use, steps are being taken to curb the use of Cr(VI) in industry, but for many manufacturing processes, Cr(VI) remains the chemical of choice, thanks to its powerful anticorrosive properties. Research on Cr(VI) is ongoing, but there are still many questions to be answered about the human health effects of this industrial heavyweight. However, with a growing base of results from recent studies, the ever-expanding field of molecular epidemiology, and growing cooperation between industry, research, and regulatory agencies, maybe it won't take another 100 years to find the answers.

Hexavalent Chromium: One Town's Story

On 7 December 1987, officials from Pacific Gas and Electric Company (PG&E), the world's largest utility, advised California regulatory authorities that they'd detected hexavalent chromium (Cr[VI]) at levels of 580 micrograms per liter (µg/L)--over 10 times the state's 50-µg/L limit for total chromium in a groundwater monitoring well. Cr(VI) was being used as an anticorrosive in the cooling towers of a PG&E gas compressor station in the Mojave Desert town of Hinkley.

People who lived in Hinkley had experienced a disturbing array of health problems: liver, heart, respiratory, and reproductive failure, cancer of the brain, kidney, breast, uterus, and gastrointestinal system, Hodgkin disease, frequent miscarriages, and more. Were these problems related to the compressor station's wastewater ponds? PG&E officials said no. But

until 1972, PG&E had knowingly released 370 million gallons of Cr(VI)-contaminated wastewater into the unlined ponds, and the toxic compound had made its way into Hinkley's groundwater.

In 1993, 77 Hinkley plaintiffs filed a lawsuit against PG&E. The suit was a direct result of a massive communications effort mounted by Erin Brockovich, an employee in a local law firm. She had uncovered the utility's environmental misconduct and launched a personal investigation that ended in the largest settlement on record for a civil class-action lawsuit. PG&E filed a motion to strike all claims for preconception injuries (fear of cancer) as speculative. But the plaintiffs--648 by the end--ended up recovering for injury claims and settling with PG&E for $333 million. In addition, PG&E agreed to stop using Cr(VI) and clean up the contamination.

The case remains controversial among chromium experts because most of the Hinkley exposures involved drinking Cr(VI)-laced water. This route of exposure is widely believed to cause much less toxicity than inhalational exposures because ingested Cr(VI) is converted to inactive trivalent chromium in the stomach. Many experts also claim that the exposures were too low to cause health effects, and that there are few data linking Cr(VI) exposures to the Hinkley residents' symptoms. But others counter that there are too many gaps in the data on chromium to dismiss the Hinkley residents' case. They believe the fact that this toxic form of chromium can enter all types of cells means that scientists may yet discover that it can damage many organ systems. Until more is known about how different doses and routes of exposure of Cr(VI) affect different populations, it is too soon to rule out high drinking water exposures as a health risk.