

Metals

Introduction

Metals are naturally occurring elements that readily form positively charged ions. Metals are found in air, food, and water. They exist primarily as salt compounds in food and water, but may also be present as oxide dusts or elemental fumes in air. Metals are used in many industrial processes and some metals are released into the air as by-products of combustion. The metals that have been studied most frequently in relation to breast cancer include cadmium, chromium, lead, and nickel. Biological and other evidence supports the plausibility that exposures to cadmium, chromium, lead, or nickel compounds could be associated with breast cancer. These heavy metals are considered known or probable human carcinogens and also have demonstrated estrogenic properties. Evidence for an association between breast cancer and exposure to other metals—including arsenic, cobalt, and mercury—has been inconsistent across studies. Although there were some positive findings, the overall evidence is weak. Exposure to zinc may be protective against breast cancer. There are few epidemiologic studies evaluating exposure to metals and breast cancer, and most of these are limited in power due to small numbers of subjects and have been published very recently; but the findings to date are intriguing and highlight the need for future studies.

Concept/Exposure Definition

Environmental Exposures

Metals are widely distributed elements, usually occurring at low levels in the earth's crust, although some geographic areas have naturally high levels in soil. Metals are released into the environment during mining operations, industrial

and manufacturing processes, and as by-products of combustion.¹⁻³ Metals are generally present at low concentrations in ambient air, although much higher concentrations have been measured near metal processing facilities.¹⁻³ The overall median air concentration at 20 monitoring sites in California from 2000–2002 was 3 ng/m³ for total chromium, 7 ng/m³ for lead and 3 ng/m³ for nickel.⁴ The median concentrations for arsenic and cadmium were around 0.5 ng/m³, based on the most recent air monitoring data in California during the 1990s.⁴ Drinking water, especially groundwater and well sources, can also be contaminated with metals. Testing in California from over 6,700 drinking water sources between 2002–2005 found that arsenic concentrations exceeded the new maximum contaminant level (10 µg /L) in about 10 percent of sources and chromium concentrations exceed recommended levels (1 µg /L) for over 33 percent of sources.⁵ Lead contamination of drinking water is a result of leaching from pipes in the home. Lead levels in California tap water are not well known, due to a lack of testing. For most metals, food is the primary source of exposure for the general population. Duplicate diet analyses conducted in the National Human Exposure Assessment Surveys (NHEXAS) in Maryland and Arizona found median daily intake rates of 30–50 µg /day for arsenic, 10–23 µg/day for cadmium, 100 µg /day for chromium, 8–15 µg /day for lead and 214 µg /day for nickel.^{6,7} Assuming standard breathing and water consumption rates, the average dietary intake of these metals is about an order of magnitude higher than intake from drinking water, and several orders of magnitude greater than the intake from air. However, the metabolism and toxicity of a chemical can vary significantly by exposure route.

Cigarette smoke is another source of exposure to metals, including cadmium,^{8,9} lead,⁹ and nickel.¹⁰ For example, smokers may double their daily intake of cadmium, compared with nonsmokers.¹ Urinary levels of cadmium¹¹ and lead¹² were also elevated among people exposed to second-hand smoke.

Occupational Exposures

Occupational exposure to heavy metals occurs in several industries. Concentrations in workplace air can be up to two orders of magnitude higher than ambient levels experienced by the general population.¹³ Metal workers are exposed to cadmium, chromium, and nickel fumes during plating operations.^{1, 14, 15} Welders had significantly higher levels of cadmium, chromium, lead, and nickel in both their blood and urine than controls who were not exposed to welding fumes during work.¹⁶ Battery manufacturing workers are exposed to cadmium, lead, and nickel salts used in production.¹ Bridge and auto body painters had higher levels of blood lead and urinary cadmium and chromium than unexposed controls.^{17, 18} Workers employed in paint and pigment manufacturing are also expected to have higher exposure to metals, due to the use of these compounds in the products they produce.¹

Extent of Human Exposures

Laboratory techniques are available to quantify metals in a variety of biologic media, including urine, blood, hair, and toenails to evaluate exposure levels. Urine concentrations provide a good measure of cumulative lifetime exposure to cadmium.¹⁹ The National Health and Nutrition Examination Survey (NHANES), a representative sample of about 5,000 persons each year around the United States, observed a median urinary cadmium concentration of 0.3 µg /g creatinine for

people 20 years of age and older during the 1999–2002 survey.²⁰ Occupational cadmium exposure can produce urinary levels as high as 50 µg /g creatinine and the occupational level of concern in the United States is set at 3 µg /g creatinine.¹ However, the occupational level of concern is based on renal damage and does not include consideration of breast cancer or hormonal mechanisms relevant to breast cancer.

Chromium levels in urine are considered a marker of recent exposure and a population-based median reference value of 0.4 µg /g creatinine was identified in the late 1980s.²¹ More recent population-based measurements in Germany found a median level of 0.1 µg /g creatinine for chromium.²² Occupational exposure studies of urinary chromium levels have observed median concentrations of 5 µg /g creatinine for boilermakers²³ and 20 µg /g creatinine for welders.¹⁶ In the general population, average nickel concentrations in urine range from 1 to 3 µg /g creatinine.²⁴ Urinary nickel concentrations resulting from occupational exposure range from 4 µg/g creatinine for welders¹⁶ to 11 µg/g creatinine among exposed refinery workers.²⁵

Whole blood is the most commonly measured biologic media for evaluating exposure to lead. Geometric mean blood lead levels among adults in the United States have declined dramatically over the past 25 years, from 12.8 µg /dL during 1976–1980 NHANES to 2.9 µg /dL during 1988–1991 NHANES, and, most recently, 1.6 µg /dL during the 1999–2002 NHANES.²⁰ The occupational level of concern in the United States is 25 µg /dL, and the highest lead exposures occur among welders, painters, and construction workers.²⁶

Critical Review of the Literature

In Vitro Studies

The mutagenicity of cadmium, chromium, lead, and nickel depends on the form, but they are generally mutagenic in either mouse lymphoma cells or the Ames Salmonella test.^{27, 28} Several heavy metal salts, including cadmium chloride, chromium chloride, and lead acetate, have been found to be estrogenic using an estrogen-receptor-dependent transcriptional expression assay or E-screen assay systems.^{29, 30} A range of estrogenicity has been observed for different species of lead and chromium, suggesting that the valence state of a metal may be an important determinant of estrogenic activity.³⁰ Chromium, lead, and nickel chlorides can also stimulate cell proliferation in the estrogen-receptor-positive human breast cancer cell line, MCF-7, through the formation of a high-affinity complex with the hormone-binding domain of the estrogen receptor.³¹

In Vivo Studies

Cadmium, chromium, lead, and nickel compounds have been shown to be carcinogenic in numerous rodent studies, producing excess lung, liver, and kidney tumors.²⁷ Cadmium chloride also has exhibited potent estrogen-like activity in ovariectomized rats, increasing uterine wet weight and promoting an increase in the side branches and alveolar buds in the mammary gland.³² This study also found that *in utero* exposure to cadmium chloride mimicked the effects of estrogen by causing an earlier onset of puberty and increasing the number of terminal end buds in the mammary gland of female offspring. In female mice infected with murine mammary tumorvirus, chromium and selenium have interactive effects on mammary tumor development and growth.

Chromium counteracts the inhibitory effect of selenium on tumor development and shortens the tumor latency period.³³

Studies in Humans

Hexavalent chromium and nickel oxide dusts are classified as known human carcinogens, while cadmium and organic lead compounds are considered probable human carcinogens.²⁸ These cancer classifications are based primarily on associations with increased rates of lung cancer in occupationally-exposed individuals. Several recently-published studies, although limited in power due to small numbers of subjects, have observed elevated levels of metals in women with breast cancer, compared to controls. Higher levels of cadmium, chromium, lead, and nickel were found in 20 breast cancer tissue biopsies than were present in eight healthy biopsies, suggesting that accumulation of these metals in breast tissue may be closely related to the malignant growth process.³⁴ A study in India found higher levels of lead and cadmium in both blood and breast tissue of 25 women with malignant breast lesions, compared to 25 women with benign breast lesions.³⁵ Cadmium levels in urine were compared between 24 women with breast cancer and 254 age-matched controls.³⁶ Women in the highest quartile of creatinine-adjusted cadmium level had more than twice the breast cancer risk (OR = 2.3, 95% CI = 1.3–4.2) of women in the lowest quartile, after adjustment for established breast cancer risk factors. There was also a statistically significant ($P_{\text{trend}} = 0.01$) increase in risk with increasing cadmium level in this study. It is not known whether increased biological levels of metals are causal factors for breast cancer, or a reflection of the disease state or treatment.

A case-control study of breast cancer and metal exposure based on an assessment of occupation using mortality records found an increased risk for women exposed to a group of metals (chromium, arsenic, beryllium, and nickel), as well as exposure to lead and cadmium individually.³⁷ The odds ratios were approximately 1.1, after adjusting for socioeconomic status for each metal exposure group, and were either significant or borderline significant for both probability and level of exposure in both white and black women. The limitations of this study include (1) an inability to control for most recognized breast cancer risk factors, and (2) potential exposure misclassification, resulting from the use of a job exposure matrix based on occupation and industry codes instead of task-based personal interviews.

An ecological study in Texas, which utilized Toxics Release Inventory data to estimate exposure to numerous pollutants, found significantly higher ($p < 0.01$) breast cancer rates in counties with reported releases of chromium and nickel, but not arsenic or cadmium.³⁸

Although the results of this study are provocative, the exposure assessment methods used the county of residence, which is a poor estimate of proximity to chemical releases. The study did not utilize the volume of reported releases to estimate the magnitude of exposure and test for a trend with increasing exposure.

Intake of certain essential metals may be protective against breast cancer. A case-control study of dietary intake conducted in Germany observed a significant protective effect for breast cancer risk between the highest quartile of zinc intake and the lowest (OR = 0.35), and a significant trend ($p < 0.01$) with increasing zinc intake.³⁹ Although selenium intake has been

shown to be protective against some types of cancer, there does not appear to be an association with breast cancer.⁴⁰

In summary, recent studies in humans suggest that there may be a relationship between exposure to certain metal compounds and the risk of breast cancer, but these studies have been limited by small numbers of exposed subjects, a lack of information on speciation of metals (salts, oxide dusts, or metal fumes), and potential exposure misclassification.

Future Directions

Given that there is widespread exposure to several metals that are likely to cause other types of cancer in humans and that these compounds are estrogenic, more breast cancer studies of cadmium, chromium, lead, and nickel are warranted.

Some first steps might include:

- Occupational studies to monitor breast cancer incidence rates in occupations with exposures to cadmium, chromium, lead, and nickel, along with better characterization of exposures to these metals by job type and task.
- A prospective study evaluating biological levels of these metals in blood or urine and the associated breast cancer risk. Metals are easily measured in blood or urine. Due to their persistence, a single biological measurement is likely to be representative of exposure levels over a relatively long period of time.
- Since the existing human evidence of a relationship between exposure to metals

and breast cancer is weak, a prospective case-control study of breast cancer that accounts for environmental exposures to potentially carcinogenic metals by all major pathways (air, water, or diet) is needed.

References

1. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Cadmium. Washington, DC, USA: United States Department of Health and Human Services (DHHS), 1999. Available at <http://www.atsdr.cdc.gov/toxprofiles/tp5-p.pdf>.
2. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Chromium. Washington, DC, USA: United States Department of Health and Human Services (DHHS), 2000. Available at <http://www.atsdr.cdc.gov/toxprofiles/tp7.pdf>.
3. Agency for Toxic Substances and Disease Registry (ATSDR). Draft Toxicological Profile for Lead. Washington, DC, USA: United States Department of Health and Human Services (DHHS), 2005. Available at <http://www.atsdr.cdc.gov/toxprofiles/tp13.pdf>.
4. California Air Resources Board (ARB), Air Quality, Emissions and Modeling Section. Annual Toxics Summaries [web page]. Sacramento, CA, USA: California Air Resources Board (ARB), 2007. Available at <http://www.arb.ca.gov/adam/toxics/statesubstance.html>. Accessed 10 Jan 2007.
5. California Department of Health Services (CDHS), Division of Drinking Water and Environmental Management (DDWEM). Chemical Contaminants in Drinking Water [web page]. Sacramento, CA, USA: California Department of Health Services, 2004. Available at <http://www.dhs.ca.gov/ps/ddwem/chemicals/default.htm>. Accessed 14 Dec 2006.
6. Ryan PB, Scanlon KA, MacIntosh DL. Analysis of dietary intake of selected metals in the NHEXAS-Maryland investigation. *Environ Health Perspect*. 2001, 109(2):121-8.
7. Moschandreas DJ, Karuchit S, Berry MR, O'Rourke MK, Lo D, Lebowitz MD, Robertson G. Exposure apportionment: ranking food items by their contribution to dietary exposure. *J Expo Anal Environ Epidemiol*. 2002, 12(4):233-43.
8. Lugon-Moulin N, Martin F, Krauss MR, Ramey PB, Rossi L. Cadmium concentration in tobacco (*Nicotiana tabacum* L.) from different countries and its relationship with other elements. *Chemosphere*. 2006, 63(7):1074-86.
9. Pappas RS, Polzin GM, Watson CH, Ashley DL. Cadmium, lead, and thallium in smoke particulate from counterfeit cigarettes compared to authentic US brands. *Food Chem Toxicol*. 2007, 45(2):202-9.
10. Torjussen W, Zachariassen H, Andersen I. Cigarette smoking and nickel exposure. *J Environ Monit*. 2003, 5(2):198-201.
11. Willers S, Gerhardsson L, Lundh T. Environmental tobacco smoke (ETS) exposure in children with asthma: relation between lead and cadmium, and cotinine concentrations in urine. *Respir Med*. 2005, 99(12):1521-7.
12. Mannino DM, Albalak R, Grosse S, Repace J. Second-hand smoke exposure and blood lead levels in U.S. children. *Epidemiology*. 2003, 14(6):719-27.

13. Hemminki K, Vainio H. Human Exposure to Potentially Carcinogenic Compounds . In: Berlin A, Draper M , Hemminki K, Vainio H, editors. *Monitoring Human Exposure to Carcinogenic and Mutagenic Agents: Proceedings of a Joint Symposium held in Espoo, Finland, 12-15 December 1983 (IARC Scientific Publications No. 59)*. Lyon, France: International Agency for Research on Cancer (IARC), 1984; pp. 37-45. (ISBN: 978-92-8321-159-4)
14. Arena VC, Costantino JP, Sussman NB, Redmond CK. Issues and findings in the evaluation of occupational risk among women high nickel alloys workers. *Am J Ind Med*. 1999, 36(1):114-21.
15. Babu KR, Rajmohan HR, Rajan BK, Kumar KM. Plasma lipid peroxidation and erythrocyte antioxidant enzymes status in workers exposed to cadmium. *Toxicol Ind Health*. 2006, 22(8):329-35.
16. Botta C, Iarmarcovai G, Chaspoul F, Sari-Minodier I, Pompili J, Orsiere T, Berge-Lefranc JL, Botta A, Gallice P, De Meo M. Assessment of occupational exposure to welding fumes by inductively coupled plasma-mass spectroscopy and by the alkaline Comet assay. *Environ Mol Mutagen*. 2006, 47(4):284-95.
17. Conroy LM, Menezes-Lindsay RM, Sullivan PM, Cali S, Forst L. Lead, chromium, and cadmium exposure during abrasive blasting. *Arch Environ Health*. 1996, 51(2):95-9.
18. Vitayavirasuk B, Junhom S, Tantisraanee P. Exposure to lead, cadmium and chromium among spray painters in automobile body repair shops. *J Occup Health*. 2005, 47(6):518-22.
19. Jarup L, Berglund M, Elinder CG, Nordberg G, Vahter M. Health effects of cadmium exposure--a review of the literature and a risk estimate. *Scand J Work Environ Health*. 1998, 24 Suppl 1:1-51.
20. United States Centers for Disease Control and Prevention (CDC). *Third National Report on Human Exposure to Environmental Chemicals*. Atlanta, GA, USA: National Center for Environmental Health, Division of Laboratory Sciences, 2005. Report ID: NCEH Pub. No. 05-0570. Available at <http://www.cdc.gov/exposurereport/3rd/pdf/thirdreport.pdf>.
21. Iyengar V, Woittiez J. Trace elements in human clinical specimens: evaluation of literature data to identify reference values. *Clin Chem*. 1988, 34(3):474-81.
22. Seifert B, Becker K, Hoffmann K, Krause C, Schulz C. The German Environmental Survey 1990/1992 (GerES II): a representative population study. *J Expo Anal Environ Epidemiol*. 2000, 10(2):103-14.
23. Mukherjee S, Rodrigues E, Aeschliman DB, Houk RS, Palmer LJ, Woodin MA, Weker R, Christiani DC. Urinary metal and polycyclic aromatic hydrocarbon biomarkers in boilermakers exposed to metal fume and residual oil fly ash. *Am J Ind Med*. 2005, 47(6):484-93.
24. Templeton DM, Sunderman FW Jr, Herber RF. Tentative reference values for nickel concentrations in human serum, plasma, blood, and urine: evaluation according to the TRACY protocol. *Sci Total Environ*. 1994, 148 (2-3):243-51.
25. Werner MA, Thomassen Y, Hetland S, Norseth T, Berge SR, Vincent JH. Correlation of urinary nickel excretion with observed 'total' and inhalable aerosol exposures of nickel refinery workers. *J Environ Monit*. 1999, 1(6):557-62.
26. Hipkins KL, Materna BL, Payne SF, Kirsch LC. Family lead poisoning associated with occupational exposure. *Clin Pediatr (Phila)*. 2004, 43(9):845-9.
27. Gold LS, Zeiger E, editors. *Handbook of Carcinogenic Potency and Genotoxicity Databases*. New York, NY, USA: CRC Press, 1997.

28. United States Environmental Protection Agency (US EPA), Office of Research and Development. Integrated Risk Information System (IRIS) Homepage [web page]. Atlanta, GA, USA: United States Environmental Protection Agency (US EPA), 2007. Available at <http://www.epa.gov/iris/>. Accessed 2007.
29. Stoica A, Katzenellenbogen BS, Martin MB. Activation of estrogen receptor-alpha by the heavy metal cadmium. *Mol Endocrinol*. 2000, 14(4):545-53.
30. Choe SY, Kim SJ, Kim HG, Lee JH, Choi Y, Lee H, Kim Y. Evaluation of estrogenicity of major heavy metals. *Sci Total Environ*. 2003, 312(1-3):15-21.
31. Martin MB, Reiter R, Pham T, Avellanet YR, Camara J, Lahm M, Pentecost E, Pratap K, Gilmore BA, Divekar S, Dagata RS, Bull JL, Stoica A. Estrogen-like activity of metals in MCF-7 breast cancer cells. *Endocrinology*. 2003, 144(6):2425-36.
32. Johnson MD, Kenney N, Stoica A, Hilakivi-Clarke L, Singh B, Chepko G, Clarke R, Sholler PF, Lirio AA, Foss C, Reiter R, Trock B, Paik S, Martin MB. Cadmium mimics the in vivo effects of estrogen in the uterus and mammary gland. *Nat Med*. 2003, 9(8):1081-4.
33. Schrauzer GN. Interactive effects of selenium and chromium on mammary tumor development and growth in MMTV-infected female mice and their relevance to human cancer. *Biol Trace Elem Res*. 2006, 109(3):281-92.
34. Ionescu JG, Novotny J, Stejskal VD, Latsch A, Blaurock-Busch E, Eisenmann-Klein M. Increased levels of transition metals in breast cancer tissue. *Neuro Endocrinol Lett*. 2006, 27(Suppl1).
35. Siddiqui MK, Jyoti, Singh S, Mehrotra PK, Singh K, Sarangi R. Comparison of some trace elements concentration in blood, tumor free breast and tumor tissues of women with benign and malignant breast lesions: an Indian study. *Environ Int*. 2006, 32(5):630-7.
36. McElroy JA, Shafer MM, Trentham-Dietz A, Hampton JM, Newcomb PA. Cadmium exposure and breast cancer risk. *J Natl Cancer Inst*. 2006, 98(12):869-73.
37. Cantor KP, Stewart PA, Brinton LA, Dosemeci M. Occupational exposures and female breast cancer mortality in the United States. *J Occup Environ Med*. 1995, 37(3):336-48.
38. Coyle YM, Hynan LS, Euhus DM, Minhajuddin AT. An ecological study of the association of environmental chemicals on breast cancer incidence in Texas. *Breast Cancer Res Treat*. 2005, 92(2):107-14.
39. Adzersen KH, Jess P, Freivogel KW, Gerhard I, Bastert G. Raw and cooked vegetables, fruits, selected micronutrients, and breast cancer risk: a case-control study in Germany. *Nutr Cancer*. 2003, 46(2):131-7.
40. Navarro Silvera SA, Rohan TE. Trace elements and cancer risk: a review of the epidemiologic evidence. *Cancer Causes Control*. 2007, 18(1):7-27.