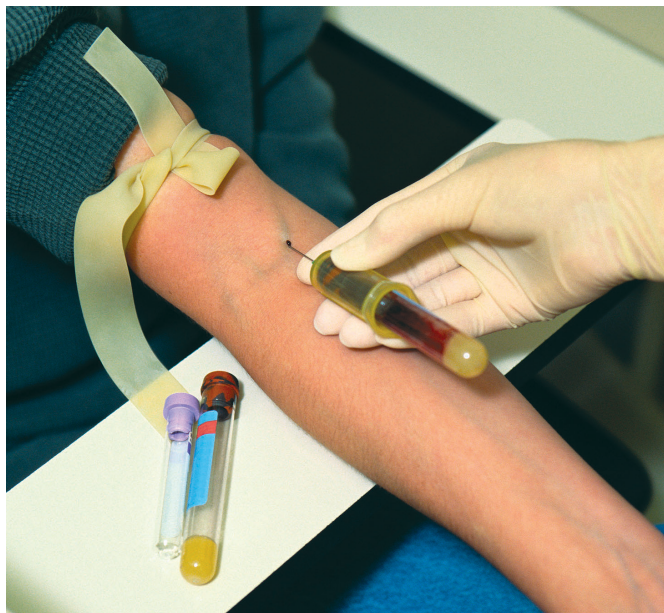


How Arsenic Acts Evidence of Oxidative Stress

Scientists have known that people chronically exposed to excessive levels of arsenic in drinking water can suffer skin sores, hypertension, and peripheral vascular disease, plus have a higher risk for certain cancers. Arsenic's mechanism of action in human illness has been unclear, but laboratory studies of cells and animals have shown that exposure to arsenic causes oxidative stress, a condition that damages cellular health and is a culprit in the development of many diseases. This month, a group of Chinese, Japanese, and U.S. scientists led by Jingbo Pi of the University of Tsukuba in Japan provide evidence that exposure to arsenic in drinking water results in oxidative stress in humans as well [*EHP* 110:331–336].

The team studied 43 residents in Wuyuan, Inner Mongolia, China. The study subjects, all members of the Han nationality, received their main arsenic exposure through groundwater, having drunk tube-well water for a mean duration of about 18 years.

The high-exposure group included 33 residents of Yindingtu and Shiba, two villages where tests of tube-well water showed that, at 0.41 mg/L, mean concentrations of inorganic arsenic were about 8.2 times higher than China's regulatory limit for drinking water and 41 times higher than the World Health Organization's guidelines for drinking water. These subjects showed various com-



Arsenic investigation. Studies of blood serum of people in China with a history of drinking arsenic-contaminated well water revealed that arsenic acts by inducing oxidative stress.

mon symptoms of arsenic poisoning, including unusual loss or overgrowth of pigmentation, hyperkeratosis (a thickening of the outer skin), higher rates of peripheral vascular disorder, peripheral neuropathy, and liver swelling. The low-exposure comparison group included 10 residents from the village of Shahe, 35 miles away, who drank tube-well water with much lower arsenic concentrations (0.02 mg/L).

Two physicians questioned the subjects on their lifetime drinking water sources, health care history, diet, and use of alcohol and cigarettes. Two dermatologists, blinded with respect to arsenic exposure in the study participants, conducted physical examinations. Blood was drawn from the study participants, and serum was separated to measure lipid peroxide levels.

The team found that participants in the high-exposure group had significantly higher levels of lipid peroxide in serum—24.0% higher—compared to the low-exposure group. Lipid peroxide is a product of lipid oxidized by free radicals, chemicals that rapidly react with other chemicals, damaging cellular DNA and playing an important role in processes such as mutagenesis, carcinogenesis, and aging. An elevated lipid peroxide profile indicates oxidative stress.

Another indicator of oxidative stress in the high-exposure group was the subjects' nonprotein sulfhydryl (NPSH) mean concentration in whole blood. NPSH plays an important role in protecting against damage by free radicals—approximately 95% of NPSH is the antioxidant glutathione, which can scavenge free radicals, or bring about enzymatic and chemical changes that trap free radicals before they damage DNA and RNA. The high-exposure group showed mean blood NPSH concentrations that were 57.3% of those in the low-exposure group.

The authors suggest that NPSH depletion might have encouraged lipid peroxides to proliferate in the high-exposure group, or the subjects' NPSH might have become depleted because of overproduced free radicals caused by exposure to arsenic. While the precise mechanism needs further study, chronic exposure to arsenic in drinking water was clearly shown to induce oxidative stress.—**John Tibbetts**

POP Surprise Wood Preservative Persists in Plasma

Exposure to low concentrations of polychlorinated biphenyls (PCBs) in the womb has been linked with adverse neurodevelopmental effects in humans and animals. It has been hypothesized recently that hydroxylated PCB metabolites, or HO-PCBs, may be the actor behind these adverse effects. So Courtney D. Sandau, formerly of Carleton University in Ottawa, and a team of Canadian scientists set out to evaluate the potential health effects of in utero exposure to HO-PCBs and other halogenated phenolic compounds [*EHP* 110:411–417]. Although HO-PCBs were indeed correlated with signs of thyroid disruption, another phenolic compound turned out to be the surprise leader in terms of how commonly it showed up in cord blood samples.

Because the symptoms of PCB exposure can overlap with those of thyroid dysfunction, several investigators have speculated that the neurologic consequences of incidental exposure to PCBs are caused by thyroid disruption. Sandau and colleagues hypothesize that HO-PCBs may play a critical role in this effect. These metabolites have very high binding affinities to transthyretin, the protein that transports thyroid hormones across the blood–brain barrier to the developing brain; in fact, they can have up to 12 times the binding affinity of thyroxine, the ligand that normally binds to this protein. Although PCB concentrations have been previously measured in umbilical cord plasma, this is the first study to examine HO-PCBs and other phenolic compounds in that medium.

The scientists looked at concentrations of PCBs, a number of HO-PCBs, and other phenolic compounds such as pentachlorophenol (PCP), which also are known to have a high binding affinity for transthyretin. They measured these compounds in 10 randomly selected umbilical cord plasma samples from each of three regions in Canada. The people living in the three different regions have different diets and thus different PCB exposures. People in Québec City, Québec, have background PCB exposures similar to those of the general population of Canada. Nunavik Inuit eat seal and beluga whale blubber, which

have high PCB concentrations. Subsistence fishers along the Lower North Shore of eastern Québec eat fish, sea mammals, and seabird eggs, giving them an intermediate level of exposure. The samples came from various umbilical cord blood surveys, so there was no standard health history or other gathering of information to accompany them.

Unexpectedly, the scientists found that one of the most abundant persistent organic pollutants found in umbilical cord plasma was not an HO-PCB but the wood preservative PCP. PCP concentrations ranged from 628 to 7,680 pg/g wet weight in plasma and did not vary significantly across regions. PCP represented an average of 66–82% of the concentration of all phenolic compounds in each region. HO-PCB concentrations, as expected, made up about 10% of total PCBs.

PCP, used in wood preservatives, biocides, and disinfectants, is not banned in the United States or Canada. Other recent studies have found PCP to be the dominant phenolic compound in whole blood from Inuits as well as Latvian and Swedish fish eaters. Food is unlikely to be a major source of PCP because it is a volatile, soluble compound; it is found in air and water, but it does not accumulate in animal tissues.

Despite the small sample size, Sandau's team found a weak negative association between total phenolic compounds and free thyroxine concentrations, suggesting that PCP and HO-PCBs may alter indeed thyroid status in newborns, perhaps by disrupting thyroid hormone metabolism. The U.S. Centers for Disease Control and Prevention (where Sandau now works) and their collaborators at Laval University in Québec will be looking for confirmation of these results on a larger population later this year.

—Rebecca Renner

Lead in the Average Joe No Increase in Cancer Risk

Although classified as a possible carcinogen in humans, lead is an established carcinogen in experimental animals; the administration of inorganic lead in rats and mice has resulted in kidney, nervous system, and lung tumors. So far, however, a definitive blood lead–cancer relationship has not been established in humans. In this issue, Ahmedin Jemal of the National Cancer Institute and his colleagues investigated the association between blood lead concentrations and cancer mortality among Caucasians (whites) in the general U.S. population [*EHP* 110:325–329]. Although a mild dose–response relationship was noted among women with very high blood lead concentrations, none of the site-specific cancers examined showed a statistically significant increase in risk with chronic lead exposure.

Many of the epidemiologic studies that relate lead with cancer have been conducted in occupational settings; no previous study is known to have examined the association between lead and cancer

in the general population. Jemal and colleagues used data from the National Health and Nutrition Examination Survey (NHANES) II Mortality Study of 1992, which was designed to examine the association between factors measured at baseline with overall or cause-specific mortality among a large general population. They restricted their study to whites because both blood lead concentrations and cancer deaths vary by race, and the number of deaths in other races in the Mortality Study was too small to provide reliable estimates.

The researchers investigated a total of 203 cancer deaths (117 men, 86 women) among 3,592 white people, with an average followup of 13.3 years until death from cancer. They used a statistical method known as Cox proportional hazard regression modeling to estimate dose–response relationships between blood lead and all cancer mortality. Relative risks were estimated for site-specific cancers (such as kidney tumors) by categorizing blood lead concentrations as high, medium, and low (for classification into groups only). The study also took into account nutrition, consumption of alcoholic beverages, and tobacco use.

A statistical test of data from the followup period indicated that cancer risks did not increase with increasing blood lead concentrations among men and women combined and among men alone, but there was a marginally significant increase among women alone. Women seemed to show a possible threshold effect at about the 94th percentile of lead, which corresponds to a blood concentration of 24 µg/dL among all study subjects. Further evaluation among women, however, showed virtually similar relative risks.

With respect to the association of blood lead concentration with selected site-specific cancer mortality, none of the site-specific cancers showed a statistically significant excess risk with elevated concentrations. Among the combined sexes and men, risks did increase with increases in blood lead concentration, but not significantly for prostate cancers among men and brain cancers among both sexes. Among women, there was no clear pattern.

Jemal lists several limitations in the database and analyses used. For instance, in the Mortality Study, people not known to be deceased were assumed to be alive; thus, a misclassification of vital status was possible. Also, measurement of blood lead occurred once and may not reflect cumulative exposure, but provides only an approximation. This becomes important because blood lead concentrations have been decreasing in the U.S. population, due, for instance, to the discontinued use of leaded gasoline, paint, and solder.

Whether lead causes cancer in humans is thus still not well established. The apparent dose–response relationship found in women with the highest blood lead concentrations could be either a chance finding or attributable to certain confounding factors. The authors write that this finding “has no clear biologic explanation; further studies of populations with sufficiently high lead exposure are needed to replicate the finding among women before it is believable.”—Julian Josephson



Reason to smile? A new study shows no statistically significant link between lead exposure and certain site-specific cancers in whites, but additional research is needed to confirm that the findings are truly valid.