# Arsenic and Infectious Disease

## A Potential Factor in Morbidity among Bangladeshi Children

Lower respiratory tract infection (LRTI) and diarrhea are two of the most common causes of morbidity and mortality in children under 5 years old, especially in low-income countries. A new prospective cohort study of the link between these types of infections and arsenic exposure revealed a dose-dependent increase in LRTI and diarrhea in relation to maternal arsenic exposure [***EHP* 119(5):719–724; Rahman et al.**].

Earlier studies linked prenatal arsenic exposure to increased risk of infant mortality, and infectious disease has been suggested as a potential underlying cause in these deaths. No epidemiologic studies have been conducted to support that explanation, but there is evidence from a few animal and human studies that arsenic may cause immunosuppression.

More than 50 million people in Bangladesh are believed to be chronically exposed to drinking water with arsenic concentrations exceeding the WHO standard of 10 µg/L.

The current study included 1,552 live-born infants of women enrolled during 2002–2004 in Matlab, Bangladesh. Arsenic exposure was assessed by measuring inorganic arsenic in maternal urine samples collected at gestational weeks 8 and 30. After birth, information on symptoms of LRTI and diarrhea in infants was collected at monthly home visits in which mothers recalled symptoms that had occurred over the previous 7 days.

The estimated relative risk of LRTI and severe LRTI increased by 69% and 54%, respectively, in the participants whose mothers had urinary arsenic concentrations in the highest quintile (262–977 µg/L), compared with offspring of mothers whose exposure was in the lowest quintile (less than 39 µg/L). The relative risk of diarrhea increased 20% for the highest-exposure group compared with the lowest-exposure group.

The authors observed that relative risks of LRTI and diarrhea increased irrespective of sociodemographic factors or nutritional status of the women. However, further evaluation is needed in a larger sample to evaluate possible effect modification, because the risks appeared more pronounced in low social strata.

Strengths of the study include the large sample size, the objective measure of arsenic exposure, and the followup of infants for one full year, which the authors say would reduce any influence of seasons on infection rates. Potential limitations include lack of measurements of infant exposure to arsenic, a lack of information about other potentially toxic substances in water and food, and reliance on mothers' reports of disease symptoms and signs. Given the millions of people worldwide who drink well water with elevated arsenic concentrations, the study results could have serious public health implications and, taken together with previous studies showing health effects from this exposure, emphasize the need to reduce arsenic exposure via drinking water.

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# Epigenetic Liver Damage

## Study Reveals Clues Implicating 1,3-Butadiene

The petroleum-derived substance 1,3-butadiene is a known human carcinogen that is a significant contributor to cancer risk in the United States. There is evidence it causes liver, heart, lung, and hematopoietic cancers in rodents through genetic damage. But some researchers suspect it also may induce changes through other pathways, including epigenetic alterations, which occur when the function of a gene is altered while its DNA sequence remains stable. A new study provides further evidence 1,3-butadiene may indeed cause epigenetic damage [***EHP* 119(5):635–640; Koturbash et al.**].

The authors exposed male C57BL/6J mice to inhaled 1,3-butadiene at two doses, 6.25 ppm and 625 ppm, for 2 weeks (6 hours per day, 5 days per week). The low dose is about 10–100 times higher than typical occupational and ambient exposures, respectively, while the inhalation pathway is considered the most common for human exposure. In the 5 mice exposed at each dose, the researchers found numerous dose-dependent alterations in genes linked with liver function. Compared with controls, mice in the low-dose group had 1 gene with a more than 2-fold increase in expression and 5 with a more than 2-fold decrease in expression. Mice in the high-dose group had 4 genes with a more than 2-fold increase in expression and 13 with a more than 2-fold decrease in expression. The high-dose mice also had a small but significant decrease in body weight.

The authors also found evidence of epigenetic changes that were consistent with altered gene expression in the liver. Changes in the attachment of methyl groups to DNA are a useful marker of epigenetic changes, and the researchers observed significant decreases in 5 markers of methylation in the high-dose group and smaller decreases in 4 of the 5 markers in the low-dose group. High-dose mice also had a roughly 50% decrease in another methylation indicator.

Changes in histones, proteins that help regulate gene expression, also occurred in the high-dose mice, with significant decreases in methylation based on 3 biomarkers. Expression of proteins involved in DNA methylation and histone methylation decreased while expression of a protein involved in histone demethylation increased, consistent with the observed decreases in DNA and histone methylation.

These findings fit with earlier research into epigenetic effects of other substances and are consistent with other mechanistic evidence of how such damage can play a role in the onset of various adverse health effects, the authors say. If additional studies—including studies of female mice, other mouse strains, and other animals—repeat these findings, this would indicate multiple modes of carcinogenicity for 1,3-butadiene and could lead to establishment of specific biomarkers for epigenetic damage that could be used in future toxicity and exposure assessments.

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# Passing Down Pollution

## Calculating Intergenerational Exposure to PCBs

Countries around the world began phasing out production of polychlorinated biphenyls (PCBs) in the 1970s after adverse health and environmental effects of these chemicals came to light. A new study calculating intergenerational differences in human PCB exposure now suggests some of the highest exposures occurred well after the chemicals were phased out [***EHP* 119(5):641–646; Quinn et al.**].

PCBs are manufactured organic chemicals that were used in numerous industrial applications starting in the 1920s. Although they have been phased out of production, PCBs are still being released into the environment from preexisting applications and improper disposal of products that contain them. Because of their chemical stability and transportability they bioaccumulate in the food chain, readily enter the human food supply, and pass from mother to infant *in utero* and during breastfeeding, with potentially harmful effects on the endocrine, immune, nervous, and reproductive systems.

In 2010 three authors of the current study and another colleague developed and tested a mechanistic model called CoZMoMAN that accounts for PCBs' emissions history and movement through the environment, the food chain, and the human body to predict concentrations in a population's body fat. For the present study, the authors used CoZMoMAN to calculate how PCB concentrations in fat changed over the lifetimes of hypothetical Swedish women born each decade between 1920 and 2010. They also analyzed how such factors as the age at which a woman first gives birth, the number of children she bears (parity), and whether she breastfeeds her babies affect both her PCB body burden and that of her children.

The model predicted that a woman's PCB exposure was determined primarily by when she was born. Women born in the 1960s were predicted to have the highest cumulative lifetime exposure—PCBs were already in widespread use when these women were born, and emissions peaked as they were maturing in the 1970s. However, it was women born in the 1980s who experienced the highest prenatal exposure and the highest peak concentration at any given age. Prenatal exposure to PCBs can be associated with serious neurologic and reproductive consequences.

Prenatal exposure was strongly influenced by children's birth order, whereas postnatal exposure was influenced by whether children were fed breast milk or infant formula. A mother's reproductive characteristics—specifically breastfeeding and parity—had a greater impact on her children's PCB burden than on her own, but these characteristics only appeared to matter for infants born after the PCB phaseout. Because both pre- and postnatal PCB exposures have been associated with health complications, the results suggest the health effects of PCBs are likely to persist over several more generations.

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# Window for Dioxin Damage

## Sperm Quality in Men Born after the Seveso Disaster

Animal studies demonstrate that endocrine-disrupting chemicals such as dioxin and dioxin-like compounds are particularly damaging when exposure occurs during prenatal and early-life development. A new study links dioxin exposure within this time frame in humans to reduced sperm quality in adult males [***EHP* 119(5):713–716, Mocarelli et al.**].

In July 1976, a trichlorophenol plant explosion near Seveso, Italy, resulted in dioxin contamination of the surrounding area. Thirty-nine men who were born near Seveso between March 1977 and January 1984 made up the exposed group in the current study, while 58 age-matched controls were born outside the contaminated area. Archived blood serum samples collected from the exposed men's mothers in 1976–1977 were used to estimate the men's prenatal dioxin exposure. All the men completed a health and lifestyle questionnaire and provided blood and semen samples. Blood samples were used for health screening tests, dioxin measurements, and hormone assays, and semen samples were analyzed for sperm motility, concentration, and morphology.

Exposed mothers had an estimated median serum dioxin concentration of 26.0 ppt at conception, whereas the median for the comparison group was estimated at 10.0 ppt. Twenty-one of the 39 exposed men were breastfed, which increased their median estimated total dioxin exposure to 40 ppt at 4–5 months of age, a critical time point for proliferation of Sertoli cells, which determine spermatogenic potential in adulthood.

Breastfed exposed men had significantly decreased sperm concentration, total sperm count, and total number of motile sperm in contrast to the 58 men in the comparison group. Compared with both the 36 breastfed comparison men and the 18 formula-fed exposed men, the 21 breastfed exposed men also had increased follicle-stimulating hormone and decreased inhibin B, a hormone pattern previously shown to be a marker for impaired spermatogenesis.

This is the first human study to show that dioxin exposure during development may permanently impair sperm production in adulthood. Current serum dioxin concentrations in the U.S. and European general populations of infants are far below levels that would trigger adverse effects. However, the study results may explain widespread low sperm counts in young men exposed during breastfeeding during times when background dioxin concentrations were 10–20 times higher than today. They also raise concerns for areas that are currently undergoing rapid industrial development and potential related contamination with dioxin and other endocrine-disrupting chemicals.

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**The 10 July 1976 Seveso disaster resulted in the highest dioxin exposure documented in humans and the largest cohort of dioxin-exposed women.**