Prenatal Preview

Early Bisphenol A Exposure May Spawn Late-Life Reproductive Problems

Scientists increasingly find that exposure to toxicants during critical periods of pre- and perinatal development can have long-lasting effects that increase the risk of reduced fertility, reproductive tumors, and breast cancer later in life. Some animal studies have suggested that very low doses of bisphenol A (BPA) in a range relevant to human exposures can cause abnormalities in the uterus, vagina, and ovary when those exposures occur during early development. To date, however, evidence for a carcinogenic effect of low-dose BPA on the female reproductive tract has been lacking; studies examining carcinogenic susceptibility to BPA have focused only on the mammary and prostate glands. Now a report from researchers at the NIEHS indicates that low prenatal doses of BPA in mice may cause potentially carcinogenic alterations in female reproductive tissues [*EHP* **117:879–885; Newbold et al.**].

Widespread human exposure to BPA is a cause for concern because of the compound's chemical similarity to diethylstilbestrol (DES), an antinausea drug that caused harmful reproductive effects in women whose mothers took it during pregnancy. This study used an experimental animal model (the CD-1 mouse) that has been useful in studying the effects of prenatal exposure to DES.

On gestational days 9–16, pregnant mice were injected with relatively low dosages of BPA—0.1, 1, 10, 100, or 1,000 µg/kg/day, which are considered by the authors and other researchers to be within an environmentally relevant range. When the dams' offspring reached late adulthood (16–18 months), their reproductive tissues were evaluated.

Some of the BPA-exposed offspring developed both benign and malignant lesions in late adulthood. In the pups that received 1 µg/kg/day, the incidence of benign ovarian cysts was 67%—similar to what the same team had previously observed for neonatal exposure to BPA. In addition, more severe ovarian lesions were found in the groups that received 10, 100, or 1,000 µg/kg/day but not in control animals. The occurrence of progressive proliferative lesions of the oviduct seemed to increase following BPA exposure, similar to effects seen in previous studies following prenatal exposure to DES. Because DES appears to delay the expression of genes that guide the development of the reproductive tract, the authors suggest that molecular "misprogramming" is the most likely reason for both DES- and BPA-induced lesions of the oviduct.

Malignant changes in the uterus also were found in exposed mice, although the incidence of those lesions was not statistically different from that seen in controls. In addition, more severe pathologies were observed in exposed animals but not in controls. These included atypical hyperplasia and stromal polyps of the uterus, sarcoma of the uterine cervix, and mammary adenocarcinoma.

According to the authors, this study is the first to find both benign and malignant lesions in reproductive tissues of senescent female mice exposed prenatally to BPA over a wide dosage range thought to be relevant to human exposure. The study adds to the growing body of literature showing adverse effects following developmental exposure to low doses of BPA and suggests that exposure during critical periods of fetal development may result in adverse reproductive and carcinogenic changes over the long term. –Angela Spivey

Legacy for Young Men

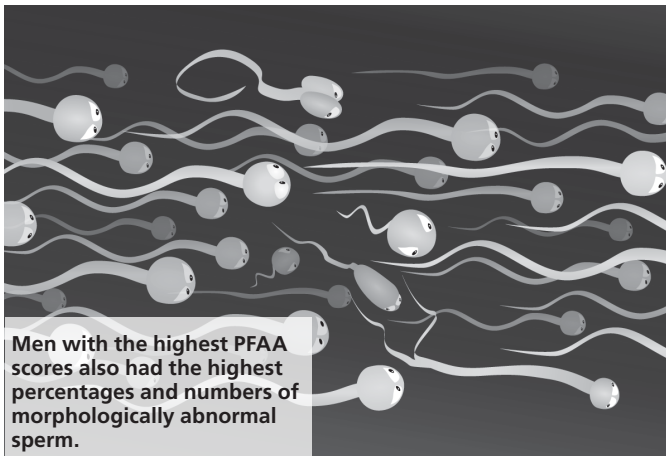
PFAAs and Human Sperm

Recent studies suggest that men's capacity for sperm production may be harmed by toxic exposures in both fetal and later life. Among the potential chemical culprits are the perfluoroalkyl acids (PFAAs), highly persistent degradation products of the polyfluorinated compounds used in products including nonstick cookware and water-resistant coatings for carpeting, clothing, and other textiles. Findings from a new Danish study suggest that exposure to PFAAs may help account for the otherwise unexplained poor semen quality observed in many young men today [*EHP* **117:923–927; Joensen et al.**].

Studies in the 1990s found that PFAAs diminished testosterone levels and increased estradiol levels in male rats. In human studies, men have appeared to have higher serum PFAA concentrations than women, and younger men may have even higher levels compared with those of older men. Young men may therefore be at higher risk for any potential adverse effects posed by these chemicals.

Inspired by such observations, the Danish team designed what they believe is the first study of the effects of PFAAs on sperm quality in humans. They focused their investigation on perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) because of these compounds' prevalence, their long half-lives, and existing evidence that they act as endocrine disruptors. The subjects included 105 young men from the general population who had provided semen samples in 2003 as part of Denmark's compulsory military draft examination. These men had the highest and lowest testosterone counts of 546 potential subjects considered. Serum levels of PFOA and PFOS were combined to give each man a PFAA score. These scores were used to classify subjects into low-, intermediate-, and high-PFAA groups.

Sperm quality varied markedly among all three groups. Compared with the low- and intermediate-PFAA groups, men in the high-PFAA group showed significantly poorer sperm quality in terms of both percentage and total numbers of morphologically normal sperm. Ejaculate from men in the low-PFAA group had a median count of 15.5 million normal sperm compared with 10 million and 6.2 million normal sperm in the intermediate- and high-PFAA groups, respectively. Average sperm concentration and motility also were lower in the high-PFAA group, but not significantly so. PFAAs were not inversely associated with testosterone levels, a finding that was contrary to expectations based on previous animal research.



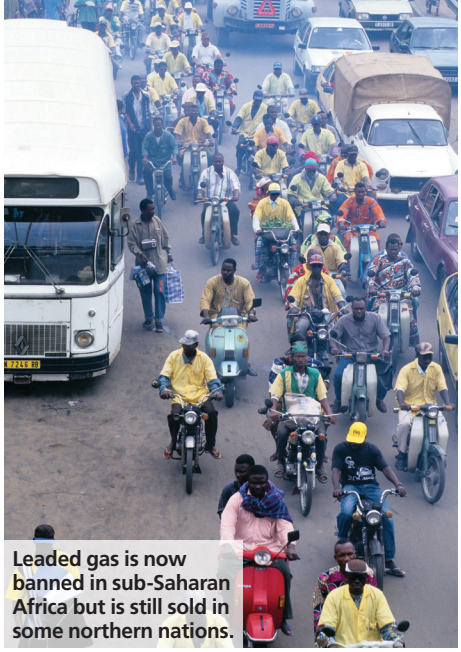
Men with the highest PFAA scores also had the highest percentages and numbers of morphologically abnormal sperm.

Daniel Cooper

The researchers note that humans and wildlife will be exposed to persistent PFAAs for years to come. They speculate that high exposures to PFAAs may be contributing to low semen quality and subfertility reported in other studies. However, they caution, results from this preliminary study should be corroborated in larger studies. –Cynthia Washam

The Price of Progress

Modern Environmental Health Hazards in Africa



Leaded gas is now banned in sub-Saharan Africa but is still sold in some northern nations.

With the spread of industrialization to all areas of the globe, scientists and policymakers alike have voiced mounting concerns over the ability of developing countries to limit the public health impacts of unchecked development. African nations, for example, have experienced rapid urbanization as well as tremendous expansion in industry and technology in an attempt to raise living standards and keep pace with the global community. But this trend has also exposed these nations to numerous modern environmental health hazards (MEHHs)—health threats that tend to accompany rapid development in the absence of health and environmental safeguards. A review of the scientific literature suggests that such hazards have added considerably to Africa's disease burden and are increasing in public health significance [*EHP* **117:863–870; Nweke and Sanders**].

The authors wrote that ongoing exposures to emerging MEHHs may soon rival the contributions of more traditional hazards—including malaria, poor access to safe drinking water, and lack of basic sanitation—that have long troubled Africa. Furthermore, poor and malnourished populations may be more vulnerable to the impacts of MEHHs, given that malnutrition increases susceptibility to toxicologic challenges. According to the United Nations Industrial Development Organization, Africa's pollution intensity (pollution generated per unit of production output) is among the highest in the world.

Reviewing published epidemiologic, exposure, and environmental studies of chemical agents, the researchers noted ongoing occupational and nonoccupational exposures to organochlorine pesticides such as DDT and to heavy metals such as lead and mercury. All these pollutants are known to persist in the environment and accumulate in the food chain over time, as confirmed by biomonitoring studies of farmworker populations in several African nations. The authors also presented evidence of existing and emerging air toxics issues related to both indoor and outdoor air pollution, pervasiveness of toxic chemicals in consumer products (such as arsenic and chromium in canned beverages), and inadequate management of domestic and industrial waste streams.

Relatively robust exposure data for lead showed elevated body burdens in African populations exposed to lead-bearing soil, dust, and paint, offering suggestive evidence of ongoing exposures to MEHHs at biological levels associated with adverse health impacts. Some studies found elevated body burdens of mercury in exposed populations such as miners, workers involved in ore processing, children who resided in mining communities, and women who habitually used soaps that contain high concentrations of inorganic mercury (such soaps are marketed as skin and hair lighteners). However, very few body burden studies have provided conclusive evidence of the relationship between heavy metal exposures and increased disease risks in African populations.

Management of MEHHs in many African nations has long been hampered by a lack of various safeguards for environmental health, such as stable institutions, adequate infrastructure, monitoring capacity, and regulatory frameworks. The researchers proposed that MEHHs should occupy a priority spot on Africa's public health and policy agenda, and emphasized that future public health policy should consider these newer environmental health risks in tandem with other longstanding public health issues. –Tanya Tillett

Fat Chance?

A High-Fat Diet May Offset the Effects of Developmental Neurotoxicity

Widespread exposure to a variety of neurotoxic chemicals has been posited as one potential factor behind what has been called a "silent pandemic" of autism spectrum disorders, learning disabilities, and other neurodevelopmental disorders. Exposure to organophosphate insecticides is of particular concern because these widely used compounds have been shown in rodents to induce persistent synaptic abnormalities in neural acetylcholine (ACh) systems at doses too low to cause symptoms of systemic exposure. Pilot studies have reported some evidence of improvement when a "ketogenic" diet—high in fat and low in carbohydrates—was used to treat certain neurologic disorders. Drawing from this preliminary clinical research, researchers have now demonstrated that many of the abnormalities in ACh systems produced by neonatal organophosphate exposure were not evident in adult rats fed a high-fat diet [*EHP* **117:916–922; Slotkin et al.**].

Rats were injected with the organophosphate parathion on each of postnatal days 1–4, at doses of 0.1 or 0.2 mg/kg/day—these dosages straddle the threshold at which cholinesterase inhibition is first detectable. In adulthood, half the animals were switched to a high-fat diet for 8 weeks. The investigators then examined brain regions of the rats to assess specific aspects of ACh synaptic function, including nicotinic ACh receptor binding, choline acetyltransferase activity, and hemicholinium-3 binding to the presynaptic choline transporter.

Adult rats on a standard lab chow diet showed multiple abnormalities in regional ACh synaptic markers following parathion exposure. All seven abnormalities observed in parathion-exposed females on the standard diet were absent in exposed females on the high-fat diet, and eight of ten abnormalities observed in parathion-exposed males on the standard diet were absent in exposed males on the high-fat diet. The results suggest that diet may offer a way to ameliorate the effects of developmental neurotoxicant exposure.

However, the authors offer several caveats. Their earlier work showed that neonatal exposure to organophosphates produced long-term changes in metabolic function that have been linked with obesity, prediabetes, and cardiovascular risk factors such as elevated serum lipids. Because these metabolic abnormalities could be exacerbated by a high-fat diet, future studies should seek to uncover whether and how specific aspects of the diet influence abnormalities in ACh systems. Moreover, although this study showed that dietary modifications may offset synaptic changes, future studies will need to determine whether such modifications can actually lead to improved neurobehavioral outcomes.

The authors also highlight a potential connection between early-life toxicant exposure and subsequent diet-related disease. If a high-fat diet can indeed ameliorate the impact of developmental neurotoxicants, then this might serve as an underlying, subconscious reinforcement to consume a high-fat diet as a way of self-remediating underlying neurobehavioral deficits—potentially expanding the public health implications of the developmental effects of neurotoxicant exposure. –Angela Spivey

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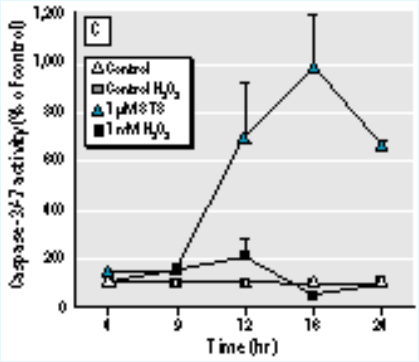
Errata

In the June Science Selection article "Prenatal Preview: Early Bisphenol A Exposure May Spawn Late-Life Reproductive Problems" [Environ Health Perspect 117:A256 (2009)], diethylstilbestrol is incorrectly identified as an antinausea drug. This drug was actually used to prevent miscarriage. *EHP* regrets the error.

In the "Discussion" (paragraph 14, p. 701) of the article by Guidotti et al. [Environ Health Perspect 115:695–701 (2007)], the first two sentences ("There appears to have been no identifiable public health impact from the elevation of lead in drinking water in Washington, DC, in 2003 and 2004. This may reflect effective measures to protect the residents, as 153 reported compliance with recommendations to filter their drinking water.") should have been replaced with the following sentence: "Measures to protect residents from exposure to lead in drinking water may have prevented more frequent elevations in blood lead." In addition, on page 695 in the right-hand column, line 4, the year 2002 should be given as 2000. The authors apologize for these errors.

In Figure 6C of Moors et al. [Environ Health Perspect 117:1131–1138 (2009)], the symbols for control and 1 µm STS were not correct. The corrected figure is presented here. *EHP* regrets the error.