Man's Worst Friend?

TCDD and Male Reproductive Effects

Animal studies indicate that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and related compounds are reproductive and developmental toxicants, but effects of human exposures are unclear. Five months after the January 1999 accidental contamination of animal feed with polychlorinated biphenyls and TCDD in Belgium, a research team collected blood and semen samples from 101 men aged 20 to 40 living in Antwerp and Peer [***EHP* 114:1670–1676; Dhooge et al.**]. The resulting analysis is the first to link exposure to TCDD and dioxin-like compounds to male reproductive effects in the general population.

Blood sample hormone analysis yielded measurements for total testosterone, luteinizing hormone, follicle-stimulating hormone, sex hormone-binding globulin, total 17β-estradiol, and inhibin B. Free testosterone was calculated from total testosterone and sex hormone–binding globulin values. Blood samples were also used to assay for compounds with the ability to bind to aryl hydrocarbon receptor, the target of TCDD; these results were expressed as a TCDD equivalent (TEQ). Semen analysis included volume, sperm concentration and morphology, and total sperm counts.

Breakfast of losers? Men who ate eggs, fish, and chicken following a food supply dioxin contamination incident showed decreased semen volume and testosterone.

Serum TCDD levels increased significantly with age and consumption of eggs, fish, and chicken. Rising TEQ values were associated with greater sperm concentration and reduced semen volume and total testosterone. These results could indicate that dioxin-like compounds decrease testosterone levels in the blood and consequently interfere with the secretory function of the seminal vesicles or prostate. The researchers saw no significant relationships between TEQ and any of the other hormone levels or with total sperm count or morphology. TEQ was also positively correlated with egg consumption, a possible reflection of the food contamination accident.

Based on their analyses, the researchers conclude that TCDD and other compounds that bind to the aryl hydrocarbon receptor do not affect sperm creation. Whether decreased gland secretion has an impact on the fertilizing capacity of the sperm cell cannot be determined from these results. **–Julia R. Barrett**

Health on the Factory Floor

Occupational Phthalate Exposure Reduces Testosterone

Human studies have shown widespread exposure to phthalates, compounds used in the manufacture of household, consumer, and medical products. The metabolites mono-2-ethylhexyl phthalate (MEHP) and mono-*n*-butyl phthalate (MBP) have shown testicular toxicity in rats, specifically damage to the cells that produce testosterone and sperm. But animal studies involve higher phthalate exposures than humans typically experience, and there is inconclusive evidence that low exposures affect testicular cells in men. Occupational phthalate exposure tends to be greater and more consistent than the highly variable low levels seen in the general population, however, and research at a Chinese manufacturing plant now reveals that such exposure can be significantly related to decreased blood testosterone concentration [***EHP* 114:1643–1648; Pan et al.**].

The study participants included 74 men who manufactured polyvinyl chloride (PVC) flooring at a plant in Liaoning Province and 63 men employed at a construction company. All the men completed a questionnaire about lifestyle factors and provided blood and urine samples. Blood samples were analyzed for circulating amounts of free testosterone, luteinizing hormone, follicle-stimulating hormone, and estradiol. Urine analysis provided data on concentrations of MBP and MEHP, which served as biomarkers of exposure.

Due to the materials involved in flooring manufacture, the men at the flooring plant were assumed to have dermal and inhalational exposure to dibutyl phthalate (DBP) and di-2-ethylhexyl phthalate (DEHP), the parent compounds of MBP and MEHP. Indeed, all the participants except one construction worker had detectable levels of urinary MBP and MEHP, demonstrating that phthalate exposure was pervasive. However, PVC plant workers had up to 100-fold higher levels of MBP and MEHP and significantly lower blood testosterone concentrations, compared with construction workers.

Lowered productivity. Men exposed to phthalates in a PVC flooring plant showed decreases in testosterone levels.

Regression analysis revealed a modest but significant decrease in testosterone as total phthalate esters increased. Based on MEHP concentrations, the investigators estimated that 40.5% of the PVC plant workers had DEHP exposure exceeding the European Union's tolerable daily intake standard of 37.0 μg/kg body weight.

The team concluded that high levels of DEHP and DBP exposure seemed to suppress testosterone production in the PVC plant workers, but it is not clear from this study what effect, if any, that might have on their fertility. **–Julia R. Barrett**

Top to bottom: Stockbyte; Digital Vision

Fetal Lead Exposure

Timing Is Everything for Effects

Many countries have set guidelines for levels of environmental lead exposure that are considered safe for children. However, relatively few studies have focused exclusively on the role of prenatal lead exposure on infant neurodevelopment. Indeed, studies conducted in the past 20 years have shown inconsistent results, perhaps because of variability in when prenatal lead was measured (first, second, or third trimester) and in what type of sample (maternal plasma, maternal whole blood, or umbilical cord blood). A comprehensive study published this month is the first to compare such variables [***EHP* 114: 1730–1735; Hu et al.**].

From 1997 to 1999, the investigators measured lead levels of 146 pregnant women living in Mexico City. Leaded gasoline was sold in Mexico City until 1997, and bone lead levels in women there are about three times higher than in the United States. The leaching of lead stored in a mother's bones provides a major source of fetal lead exposure.

The investigators obtained samples of plasma and whole blood during each trimester and umbilical cord blood at delivery. They also tested the neurodevelopment of the children at age 24 months using the Mental Development Index (MDI), which evaluates memory, language, and sensory abilities.

The authors found that lead exposure during the first trimester of pregnancy was more strongly linked to later decreases in the MDI scores than exposure during the latter two trimesters. Moreover, maternal plasma lead was the best predictor of a child's later neurobehavioral performance because most of the lead in whole blood is attached to red cells and cannot cross the placenta. Each increase of 1 standard deviation unit in plasma lead lowered the MDI score by 3.5 points. Neither maternal levels in the second or third trimester nor cord blood levels impacted MDI scores in as strong a fashion.

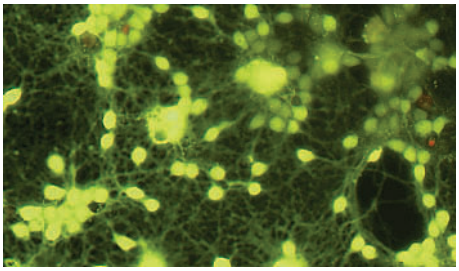
Early threat. A study of pregnant women in Mexico City showed that fetal lead exposure during the first trimester had a greater impact on later neurodevelopment than exposure in other trimesters.

The results raise two questions: should lead be routinely measured in the first trimester of pregnancy, and are there ways to reduce fetal exposure? Plasma lead is expensive and difficult to measure, according to the authors, making routine clinical testing impractical. Studies suggest that calcium supplements slow the release of lead from bone. An ongoing clinical trial of pregnant women is assessing the efficacy of this intervention. **–Carol Potera**

New Neurons at Risk

Genotoxicants and Brain Development

Neurodevelopmental disorders such as learning disabilities, mental retardation, and autism spectrum disorders affect an estimated 5–10% of the 4 million babies born in the United States annually. In a report released in 2000, the National Research Council concluded that 3% of these disorders are the direct result of environmental exposures to neurotoxicants, with another 25% arising from the interaction between such exposures and genetic susceptibility. Investigators have shown that many of these long-term adverse outcomes can be attributed to genetic damage to immature neurons in the developing brain related to exposure to genotoxicants, chemicals that disrupt the complex, delicate cellular process that regulates development of a fully functional brain. Although the precise mechanisms involved are still poorly understood, scientists are now starting to unravel the molecular ravages caused by genotoxicants [***EHP* 114:1703–1712; Kisby et al.**].



Young and vulnerable. Immature neurons called granule cells are more sensitive to genotoxicants.

As reported in this month's issue, a research group exposed cultures of immature neurons known as granule cells and the more developed and more abundant astrocytes to sublethal doses of two well-characterized alkylating genotoxicants: methylazoxymethanol (MAM), a highly toxic compound synthesized from the poison found in plants called cycads, and nitrogen mustard (HN2), a chemotherapeutic agent. The team then analyzed the cultures for cell viability, DNA damage, markers of apoptosis, and corresponding gene expression patterns. The intent of the research is ultimately to identify the key molecular networks that are targeted by genotoxicants, in order to understand how such agents influence brain development.

Results showed that granule cells were much more sensitive to the genotoxicants than astrocytes. The exposures caused dose-dependent DNA lesions that persisted and accumulated, apparently because, unlike astrocytes, granule cells lack the ability to repair DNA damage. In other words, once the exposure has wreaked havoc on the developing neurons, the damage is done, and its impact is felt throughout the process of neuronal development, leading to long-term impairment. The authors speculate that these events "could explain why the developing cerebellum is a prime target in several human neurodevelopmental disorders."

The team also discovered that the two genotoxicants affected distinctly different sets and functional types of genes. MAM targeted differentiation, stress and immune response, cell signaling, and transcriptional regulation genes, whereas HN2 targeted apoptosis and protein synthesis gene expression. This preferential targeting suggests that different genotoxicants probably cause completely different effects in the developing brain. With a significant proportion of neurodevelopmental disabilities thought to stem directly from early exposures to DNA-damaging agents or gene–environment interactions related to such exposures, further investigation of the molecular networks involved in these effects is clearly needed. **–Ernie Hood**

Top to bottom: Aubrey Wade/Panos Pictures; Kisby et al.