Breaking In through Critical Windows

**p,p’-DDE May Alter Fetal Neurodevelopment**

DDT has been widely used to control mosquito-borne malaria since the late 1940s. The compound and metabolites such as p,p’-DDE linger in the environment for decades; even in areas where DDT has been banned, these neurotoxic chemicals are still detected in human blood, fat, breast milk, and umbilical cord blood. Researchers examined the possibility that prenatal exposure to p,p’-DDE damages early neurodevelopment, and present the first evidence that exposure during a critical window of development adversely affects infant psychomotor development. [EHP 115:377–382; Torres-Sánchez et al.]

From January 2001 to June 2005, 1,585 reproductive-age women in the State of Morelos, Mexico, where DDT had been used for malaria control until 1998, were invited to join the prospective cohort study. Each woman choosing to participate provided a blood sample and information about sociodemographic characteristics, obstetric and gynecologic history, alcohol and tobacco use, occupation, and previous pesticide use.

Once a woman became pregnant, the researchers conducted in-home visits each trimester to collect a blood sample and data on her pregnancy, weight, and diet. After the woman gave birth, they evaluated her child at 1, 3, 6, and 12 months of age, focusing on health, feeding, growth, and cognitive and psychomotor development. The researchers also tested maternal intelligence and assessed the home environment by observing factors such as parent–child interaction and available toys. Data were available for 244 mother–child pairs.

p,p’-DDE was detected in all maternal blood samples. Concentrations were the highest in the third trimester, but analyses revealed that only first-trimester concentrations were associated with impaired psychomotor development. This association remained after controlling for maternal intelligence and the home environment; breastfeeding appeared to have a slight protective effect.

A subset of 105 maternal blood samples were also tested for lead. Because maternal lead concentrations were not available for all infants, lead exposure could not be completely excluded as contributing to effects correlated with first-trimester p,p’-DDE exposure. However, the low negative correlation between the two neurotoxicants made it unlikely that the effects observed were either amplified or masked by lead. There did not appear to be an association between prenatal p,p’-DDE exposure and cognitive development. These findings add to the growing evidence that DDT metabolites in a mother affect her child’s psychomotor development during infancy. The researchers suggest that prenatal p,p’-DDE exposure needs further attention, even in countries where DDT has not been used for decades. –Julia R. Barrett

Carbon Concerns

**Nanotubes Cause Cardiovascular Damage**

Lung deposition of single-wall carbon nanotubes (SWCNTs), one of the most commonly used materials in nanotechnology, is already known to cause localized toxic effects. Now scientists have demonstrated that such deposition also leads to cardiovascular damage in mice, including accelerated formation of atherosclerotic plaques [EHP 115:377–382; Li et al.]. The findings add to concerns that exposure to SWCNTs could result in systemic toxic effects.

The team conducted a series of experiments, instilling SWCNTs into the lungs of mice. In an initial screen for extrapulmonary effects, Hox-1-luc reporter transgenic mice were exposed to single SWCNT doses of 10 or 40 µg. Heme oxygenase-1 (HO-1) gene expression, a biomarker of oxidative stress, was activated in the animals’ lung, aorta, and heart tissue at 7 days post-exposure, declining to control levels by day 28. This held with pulmonary toxicity studies showing an early, transitory inflammatory response.

The same dosing scheme was used in experiments with the commonly used C57BL/6 mouse, which showed dose-dependent aortic mitochondrial DNA (mtDNA) damage at 7, 28, and 60 days post-exposure. MtDNA is highly susceptible to oxidative damage, considered to be an initiating event in atherogenesis. Among the treatment groups, glutathione and protein carbonyl levels—two other indicators of oxidative stress—were also significantly reduced and increased, respectively, adding to the evidence that exposure to SWCNTs can lead to oxidative insult. Exposure to comparable doses of ultra-fine carbon black particles in a control group produced no such damage to aortic mtDNA.

The group then tested the effects of SWCNT exposure in ApoE-/- mice, a widely used model of human atherosclerosis. They exposed the mice to 20 µg of SWCNTs once every other week for 8 weeks. Then the mice were fed either a regular chow diet or a high-fat diet for the first half of that period to induce the elevated lipid concentrations that often precede atherosclerosis. Although SWCNT exposure was not associated with changes in the animals’ lipid profiles, the exposed mice on the high-fat regimen did exhibit accelerated plaque formation in the aorta and brachiocephalic arteries compared with controls.

The researchers note that the cardiovascular effects resulting from SWCNT exposure could be either direct, as a result of translocation of particles from the lung into the systemic circulation, or indirect, caused by the release of inflammatory mediators in the lung or by altered pulmonary function (although no increase in several measured inflammatory mediators was detected in the exposed animals). Whichever mechanism may be at work, these data show that lung deposition of SWCNTs, a possible workplace exposure scenario, can cause systemic damage and may contribute to cardiovascular disease. –Ernie Hood
The Testosterone Test
Phthalate Inhibits Leydig Cell Aggregation

Testicular cancer and low sperm count are adult disorders, but evidence increasingly suggests they have a fetal origin. Cryptorchidism and hypospadias, apparent at birth, also appear linked to prebirth events. According to the testicular dysgenesis syndrome (TDS) hypothesis, all four disorders, which by some reports have become more common in recent decades, partially stem from fetal abnormalities in testosterone-producing Leydig cells. An investigation now reveals that di(2-ethylhexyl) phthalate (DEHP) and its metabolite monobutyl phthalate (MBP) suppress testosterone production in rats and primates [EHP 115:390–396; Hallmark et al.]. Attempts to establish in vitro models were unsuccessful, however.

In rats, prenatal exposure to DBP can induce Leydig cell changes and TDS-like effects. Chronic, low-level exposure to DBP and other phthalates, widely used as plasticizers, is common among humans, but it is unknown if it causes the same effects. The primary goal of the current study was to determine whether effects seen in rats could be replicated in vitro with fetal rat and human testis explants (extracted tissue maintained in culture). The team also conducted experiments in male infant marmosets, whose neonatal testosterone production mirrors that of human males.

Preliminary work revealed that rats with prenatal DBP exposure produce significantly less testosterone and had more medium or large Leydig cell clusters. This is notable because larger clusters are associated with defective testicular development. Rat fetal testis explants, however, showed only minor MBP-related effects, and results from comparable human explants were even less conclusive.

Because known in vivo reactions could not be replicated in vitro—indicating either a problem with the method or misidentification of the active metabolite—the team tested MBP in marmosets. In five sets of marmoset twins, one twin was exposed to MBP for two weeks while the other served as a control. Blood testosterone levels did not differ significantly, but Leydig cell numbers and size were consistently increased in the MBP group.

Because low testosterone triggers increased secretion of luteinizing hormone, which stimulates Leydig cell testosterone production, the researchers checked whether there was an initial MBP-associated suppression in testosterone production. They found that a single dose of MBP in newborn marmosets significantly reduced testosterone levels within hours. This finding led to the hypothesis that increased luteinizing hormone secretion compensates for an initial MBP-associated inhibition of testosterone production, which the researchers conclude should be considered in future animal studies. They also conclude that in vivo marmoset research represents the best current means for investigating the steroidogenic effects of DBP relevant to humans. –Julia R. Barrett

Metal Duo Damages Lungs
Lead and Manganese in Fine Particulates

Extensive evidence indicates that fine particulates can damage human lungs. But much remains unknown about exactly which components of these particulates are to blame. In a small study of Korean children, researchers have found that two metals, lead and manganese, are among the substances likely at fault. In a study of Korean children scientists identified some of the health-damaging components of fine particulates.

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