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* 115:435–439; Torres-Sánchez et al.**].

Back tracks. Long-ago pesticide spraying can still affect today's children.

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.

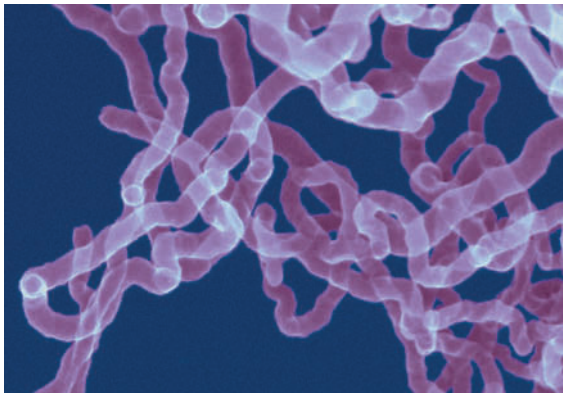
A subset of 105 maternal blood samples were also tested for lead. Because maternal lead concentrations were not available for all infants, lead exposure could not be completely excluded as contributing to effects correlated with first-trimester *p,p´*-DDE exposure. However, the low negative correlation 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.



Worming their way in? SWCNTs may cause systemic toxicity.

The team conducted a series of experiments, instilling SWCNTs into the lungs of mice. In an initial screen for extrapulmonary effects, *Ho1-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 ultrafine 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.

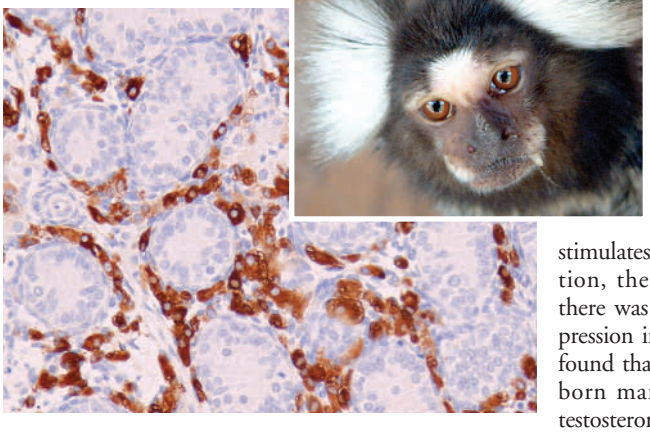
The researchers note that the cardiovascular effects resulting from SWCNT exposure could be either direct, as a result of translocation of particles from the lung into the systemic circulation, or indirect, caused by the release of inflammatory mediators in the lung or by altered pulmonary function (although 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**

Top to bottom: Aubrey Wade/Panos Pictures; Dennis Kunkel

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(*n*-butyl) phthalate (DBP) 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.



Testicular effect. The numbers and size of Leydig cells (in brown, above) increased in MBP-treated marmosets.

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 produced 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 [***EHP* 115:430–434; Hong et al.**].

To pin down the particulate culprits, the researchers evaluated 43 children who attended school on an island near Incheon City. The island has low traffic density and industrial emissions, but concentrations of fine particulates 2.5 μm in diameter or smaller were relatively high by U.S. standards, perhaps owing to natural sources or dust from China or Mongolia. The mean of 20.27 μg/m^3 measured during the six-week study period was about one-third higher than the U.S. annual standard.

After an introductory period during which the children (median age 10) learned how to use a peak expiratory flow meter to measure their lung function, each child used the device at three fixed times every day. Meanwhile, the researchers sampled fine particulates every day on the roof of a building 2 km from the school and analyzed the concentration of five metals: aluminum, iron, lead, manganese, and zinc. Previous studies have shown these metals might play either beneficial or harmful roles when present in particulates.

Gotcha! In a study of Korean children scientists identified some of the health-damaging components of fine particulates.

The researchers also tested the children for polymorphisms of *GSTM1* and *GSTT1*. These two genes play a role in the function of the enzyme glutathione *S*-transferase, which scavenges the damaging reactive oxygen species created by some metals. In addition, they took into account many other factors, including weather, day of the week, sex, age, height, weight, asthma history, passive smoking exposure at home, and socioeconomic status. They did not test for other metals, acquire data on other lung-damaging pollutants (such as nitrogen dioxide or ozone), or measure personal fine particulate exposures.

Typical of Asian populations, roughly half the children did not have one gene or the other due to deletion. The team found that lead and manganese were linked with significant reductions in peak expiratory flow rate, regardless of whether a child had either of the tested gene polymorphisms. The three other metals had no significant effects, even though they sometimes were present at much higher concentrations than lead and manganese. The team acknowledges that additional studies are needed to comprehensively determine the impact of metals on the respiratory system. **–Bob Weinhold**

Top to bottom: Marion Walker/Medical Research Council; inset: Alan Wesley/Shutterstock; Photodisc